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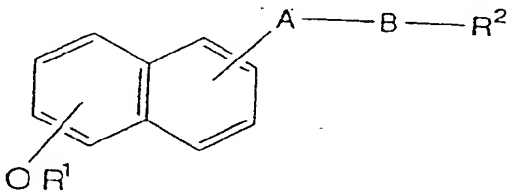
(54) Naphthyloxyacetic acid derivatives and their use as PGW2 agonists and antagonists

(57) Naphthyloxyacetic acid derivatives of the formula (I)



(I)

wherein R^1 is H, alkyl, alkylene-(-$COOH^{10}$, -OH, -$CONR^4R^5$, -$CONR^6$-alkylene-OH, -NR^4R^5, -cyano or -tetrazolyl); A is single bond, alkylene, alkenylene, -S-alkylene, -O-alkylene; B is NR^3CO, $CONR^3$; and R^2 is (1) alkyl, (2) alkenyl, (3) alkyl or alkenyl substituted by 1-3 of phenyl, cycloalkyl, naphthyl and heterocyclic ring containing nitrogen atom (said ring being substituted by 1-3 of alkyl, alkoxy and halogen etc.), (4) NR^7R^8 or (5) alkylene-NR^7R^8; and non-toxic salts and hydrates thereof can bind with the PGE_2 receptor and are useful as PGE_2 antagonists or agonists.

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Description

This invention relates to naphthyloxyacetic acid derivatives, processes for their preparation and pharmaceutical compositions containing them.

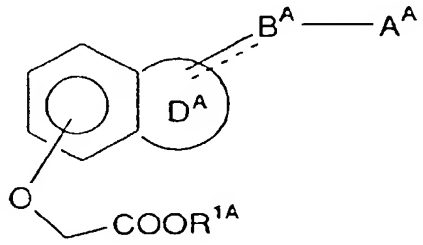
As PGE_2 agonist, many compounds have been known including PGE_2 per se. However, no compounds which antagonize PGE_2 or inhibit PGE_2 activity (PGE_2 antagonist) have been known until now.

PGE_2 has been known as a metabolite in the arachidonate cascade. Its known activities include uterine contractile activity, a pain-inducing effect, a promoting effect on digestive peristalsis, an awaking effect, a suppressive effect on gastric acid secretion, hypotensive activity and blood platelet inhibition activity. Antagonist or agonist activities on these effects would be expected to confer the following activities on a compound.

To antagonize PGE_2 means to suppress the effects above mentioned, so PGE_2 antagonists are considered to inhibit uterine contraction, to have analgesic action, to inhibit digestive peristalsis, or to induce sleep. Therefore PGE_2 antagonists are considered to be useful for the prevention of abortion, or as analgesics, antidiarrheals or sleep inducers.

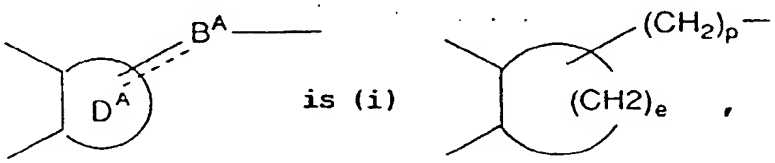
To agonize for PGE_2 means to promote the effects above mentioned, so PGE_2 agonists are considered to stimulate uterine contraction, to promote digestive peristalsis, to suppress gastric acid secretion, to lower blood pressure or to inhibit blood platelet aggregation. Therefore PGE_2 agonists are considered to be useful as abortifacients, cathartics, and antiulcer, anti-gastritis, antihypertensive or antithrombosis agents.

Japanese Patent Application Kokai Hei 6-72978 and European Patent Application EP-0542203A3 disclose that fused benzeneoxyacetic acid derivatives of the formula (A):



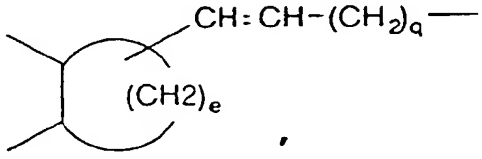
(A)

wherein

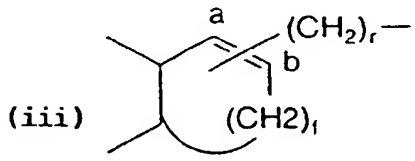


is (i)

,

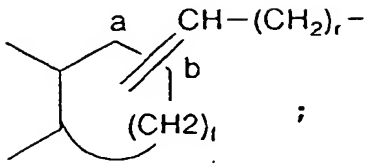


(ii) ,



(iii)

or

(iv) 

;

A^A is

(i) -COW^A,
(ii) -NR^{4A}-Y^A or
(iii) -Z^A-NR^{4A}-$CONR^{2A}R^{3A}$;

W^A is

(i) -$NR^{2A}R^{3A}$,
(ii) -NR^{4A}-OR^{5A},
(iii) -NR^{4A}-$NR^{2A}R^{3A}$ or
(iv) -NR^{4A}-N=$CR^{2A}R^{3A}$;

Y^A is

(i)-CO-R^{5A},
(ii) -CO-U^A-$NR^{2A}R^{3A}$ or
(iii) -CS-U^A-$NR^{2A}R^{3A}$;

Z^A is

(i) -CH=N- or
(ii) -CH_2-NR^{6A}-;

R^{1A} is hydrogen atom or C1-4 alkyl;

R^{2A} and R^{3A} each, independently, is

(i) hydrogen atom,
(ii) phenyl,
(iii) benzoylphenyl,
(iv) 4-7 membered, unsaturated monocyclic hetero ring containing one nitrogen atom as hetero atom or
(v) C1-4 alkyl substituted by 1-3 rings optionally selected from 4-7 membered, unsaturated monocyclic hetero ring containing one nitrogen atom as hetero atom, and phenyl;

R^{4A} is hydrogen atom, C1-6 alkyl or phenyl;

R^{5A} is

(i) phenyl,
(ii) 4-7 membered, unsaturated monocyclic hetero ring containing one nitrogen atom as hetero atom or
(iii) C1-4 alkyl subsutituted by 1-3 rings optionally selected from 4-7 membered, unsaturated monocyclic hetero ring containing one nitrogen atom as hetero atom, and phenyl;

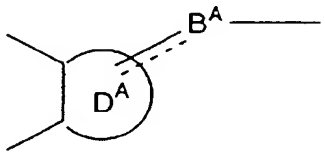
R^{6A} is hydrogen atom, C1-6 alkyl or phenyl;

U^A is single bond or C1-4 alkylene; the said phenyl and hetero rings may be also substituted by C1-4 alkyl, C1-4 alkoxy, halogen atom, nitro or trihalomethyl, when R^{2A}, R^{3A}, R^{4A}, R^{5A} or R^{6A} is phenyl or the group containing phenyl, and when R^{2A}, $R3^A$ or R^{5A} is the said hetero ring or the group containing the hetero ring;

e is integer of 3-5;

f is integer of 1-3;
p is zero or integer of 1-4;
q is zero or integer of 1-2;
r is zero or integer of 1-4;
s is zero or integer of 1-3;

with the proviso that, when A^A is (ii) -N-R^{4A}-Y^A (in which R^{4A} and Y^A are the same meaning as hereinbefore defined), q, r, or s is not zero;
and that when

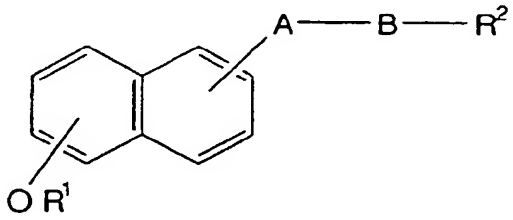


is the formula (iii) or (iv), -$(CH_2)_r$- or =CH-$(CH_2)_s$- in the side chain should be bonded to the carbon atom at the position a or b in the ring;
can bind with the PGI_2 receptor and that they are useful as medicine.

The compounds disclosed in the above Japanese Patent Application Kokai Hei 6-72978 or European Patent Application EP-0542203A3 are different in structure from the compounds of the present invention because the naphthalene ring in the basic skeleton of the former compounds is always partially saturated. It is disclosed that the activity of these compounds is as PGI_2 antagonists or agonists.

As apparent to the ordinary skilled person in the art, PGE_2 and PGI_2 belong to the common PG family, but their activities are entirely different from each other. Therefore, naturally the activities and effectiveness of the compounds which antagonize or agonize PGE_2 are different from those of the compounds which antagonize or agonize PGI_2. So, it is not possible to predict that the compounds of the present invention possess PGE_2 antagonist or agonist activities from the disclosure of Japanese Patent Application Kokai Hei 6-72978 or European Patent Application EP-0542203A3.

The present invention provides a naphthyloxyacetic acid derivative of the formula (I)



(I)

wherein

R^1 is

(i) hydrogen,
(ii) C1-4 alkyl,
(iii) (C1-4 alkylene)-$COOR^{10}$ in which R^{10} is hydrogen or C1-4 alkyl,
(iv) (C1-4 alkylene)-OH,
(v) (C1-4 alkylene) - $CONR^4R^5$ in which R^4 and R^5 each, independently, is hydrogen or C1-4 alkyl,
(vi) (C1-4 alkylene)-$CONR^6$-(C1-4 alkylene)-OH in which R^6 is hydrogen or C1-4 alkyl,
(vii) (C1-4 alkylene)-NR^4R^5 in which R^4 and R^5 are as hereinbefore defined,
(viii) (C1-4 alkylene)-cyano or
(ix) (C1-4 alkylene)-tetrazolyl,

A is a single bond, C1-6 alkylene, C2-6 alkenylene, -S-(C1-6 alkylene) or -O-(C1-6 alkylene),
B is NR^3CO or $CONR^3$ in which R^3 is hydrogen or C1-4 alkyl, and
R^2 is

(i) C1-6 alkyl,
(ii) C2-6 alkenyl,
(iii) C1-6 alkyl substituted by 1-3 substituent(s) selected from phenyl, C4-7 cycloalkyl, naphthyl and 4-7 mem-

bered heterocyclic ring containing one nitrogen atom,
(iv) C2-6 alkenyl substituted by 1-3 substituent(s) selected from phenyl, C4-7 cycloalkyl, naphthyl and 4-7 membered heterocyclic ring containing one nitrogen atom,
(v) NR^7R^8 in which R^7 and R^8 each, independently, is phenyl, C4-7 cycloalkyl, naphthyl or 4-7 membered heterocyclic ring containing one nitrogen atom, or
(vi) (C1-6 alkylene)-NR^7R^8 in which R^7 and R^8 are as hereinbefore defined,

and, when R^2 contains a phenyl, cycloalkyl, naphthyl or heterocyclic ring, said ring is unsubstituted or substituted by 1-3 substituent(s) selected from C1-4 alkyl, C1-4 alkoxy, halogen, nitro and trifluoromethyl; or a non-toxic salt, non-toxic acid addition salt or hydrate thereof.

In the formula (I), C1-4 alkyl represented by R^1, R^3, R^4, R^5, R^6 and R^{10}, and in R^2, means methyl, ethyl, propyl, butyl and isomeric groups thereof.

In the formula (I), the C1-4 alkoxy in R^2 means methoxy, ethoxy, propoxy, butoxy and isomeric groups thereof.

In the formula (I), C1-4 alkylene in R^1 means methylene, ethylene, trimethylene, tetramethylene and isomeric groups thereof.

In the formula (I), the C1-6 alkylene represented by A and in A means methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene and isomeric groups thereof.

In the formula (I), the C2-6 alkenylene represented by A means the above mentioned alkylene having 1-3 double bonds, for example vinylene, propenylene, butenylene, pentenylene or hexenylene.

In the formula (I), C1-6 alkyl represented by R^2 means methyl, ethyl, propyl, butyl, pentyl, hexyl and isomeric groups thereof.

In the formula (I), C2-6 alkenyl represented by R^2 and in R^2 means the above mentioned alkyl having 1-3 double bonds, for example, vinyl propenyl, butenyl, pentenyl or hexenyl.

In the formula (I), C4-7 cycloalkyl in R^2 means cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

In the formula (I), 4-7 membered heterocyclic ring containing one nitrogen atom in R^2 may be saturated or unsaturated. Examples of such a ring include azete, pyrrole, pyrroline, pyrrolidine, pyridine, pyridoline, pyridolidine, piperidine, azepine, azoline and azolidine.

In the formula (I), the halogen in R^2 means chlorine, bromine, fluorine and iodine.

As R^2, the group which does not contain any 4-7 membered heterocyclic ring containing one nitrogen atom, for example,

(i) C1-6 alkyl,
(ii) C2-6 alkenyl,
(iii-a) C1-6 alkyl substituted by 1-3 substituent(s) selected from phenyl, C4-7 cycloalkyl and naphthyl,
(iv-a) C2-6 alkenyl substituted by 1-3 substituent(s) selected from phenyl, C4-7 cycloalkyl and naphthyl,
(v-a) $NR^{7a}R^{8a}$ in which R^{7a} and R^{8a} each, independently, is phenyl, C4-7 cycloalkyl or naphthyl or
(vi-a) (C1-6 alkylene)-$NR^{7a}R^{8a}$ in which R^{7a} and R^{8a} are as hereinbefore defined, is preferred.

In addition, as R^2, the group which contains at least one 4-7 membered heterocyclic ring containing one nitrogen atom, for example,

(iii-b) C1-6 alkyl substituted by one 4-7 membered heterocyclic ring containing one nitrogen atom, said alkyl having no additional substituents or having one or two additional substituents selected from phenyl, C4-7 cycloalkyl, naphthyl and 4-7 membered heterocyclic ring containing one nitrogen atom,
(iv-b) C2-6 alkenyl substituted by one 4-7 membered heterocyclic ring containing one nitrogen atom, said alkenyl having no additional substituents or having one or two additional substituents selected from phenyl, C4-7 cycloalkyl, naphthyl and 4-7 membered heterocyclic ring containing one nitrogen atom,
(v-b) $NR^{7b}R^{8b}$ in which one of R^{7b} and R^{8b} is phenyl, C4-7 cycloalkyl, naphthyl or 4-7 membered heterocyclic ring containing one nitrogen atom and the other is 4-7 membered heterocyclic ring containing one nitrogen atom or
(vi-b) (C1-6 alkylene)- $NR^{7b}R^{8b}$ in which R^{7b} and R^{8b} are as hereinbefore defined, is also preferred.

Unless otherwise specified, all isomers are included in the invention.

For example, alkyl, alkylene and alkenylene may be straight-chain or branched-chain. Double bond in alkenylene incudes configurations E and Z and EZ mixtures. Isomers generated by asymmetric carbon(s) e.g. branched alkyl are also included within the present invention.

Salts, Acid addition salts and Hydrates

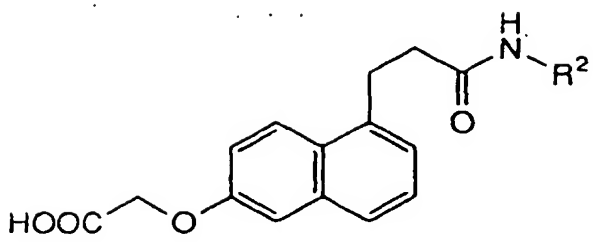
The compounds of the formula (I) may be converted into the corresponding salts by known methods. Non-toxic and water-soluble salts are preferred. Suitable salts include salts of alkali metals (e.g. potassium or sodium), salts of alkaline earth metals (e.g. calcium or magnesium), ammonium salts, salts of pharmaceutically acceptable organic amines (e.g. tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)aminomethane, lysine, arginine or N-methyl-D-glucamine).

The compounds of the formula (I) may be converted into the corresponding acid addition salts by methods known *per se*. Non-toxic and water-soluble acid addition salts are preferred. Suitable acid addition salts include salts of inorganic acids, e.g., hydrochloride, hydrobromide, sulphate, phosphate or nitrate and salts of organic acids, e.g., acetate, lactate, tartarate, oxalate, fumarate, maleate, citrate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, toluenesulphonate, isethioate, glucuronate or gluconate.

The compounds of the formula (I) and salts thereof may be converted into hydrates thereof by methods known *per se*.

Particularly preferred compounds of the formula (I) of the present invention are the compounds described in the Examples and the following Tables 1-49.

Table 1



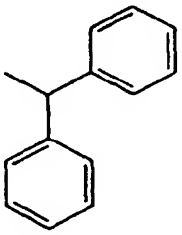
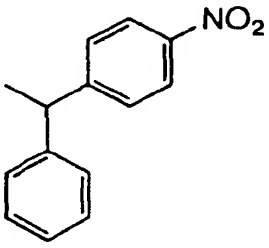
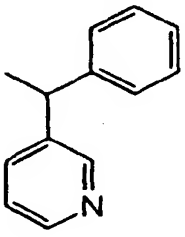
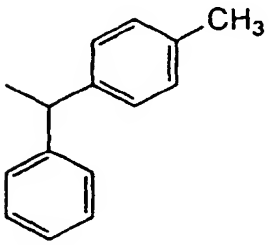
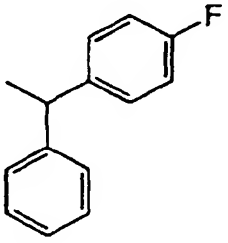
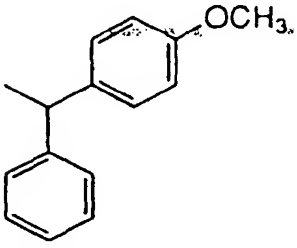
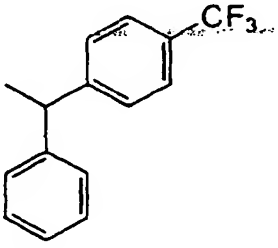
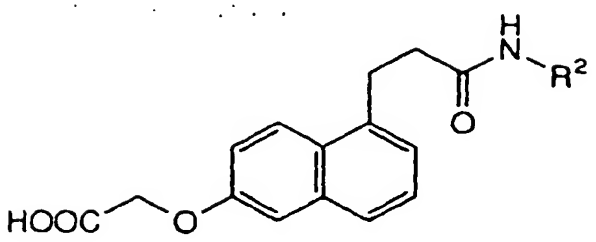
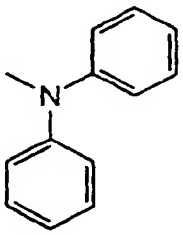
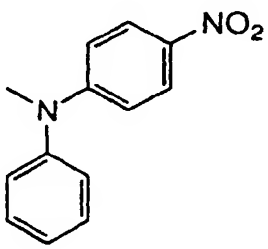
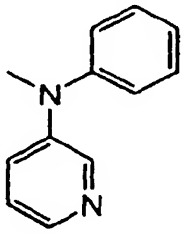
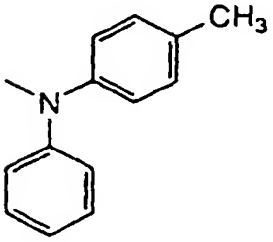
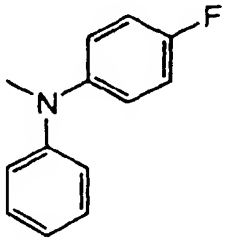
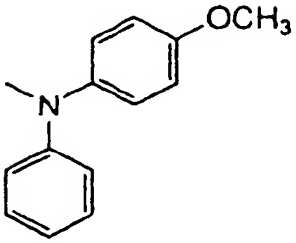
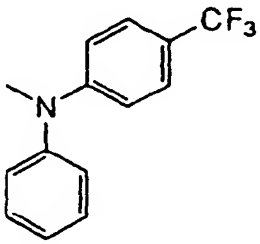
R^2








Table 1 (Continued)



R^2








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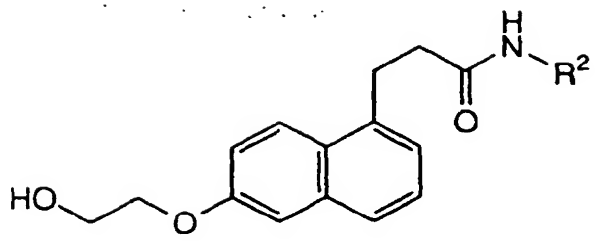
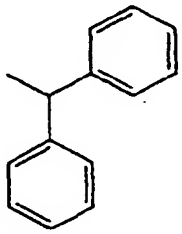
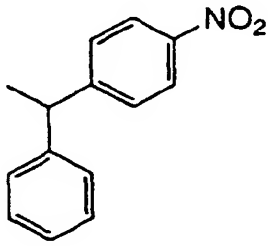
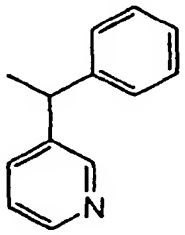
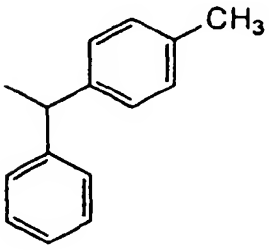
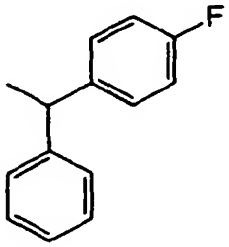
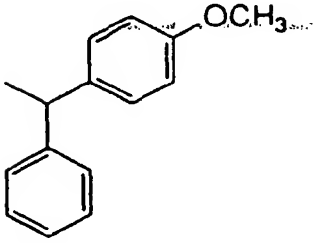
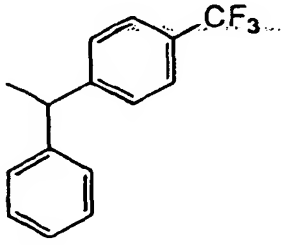


R^2








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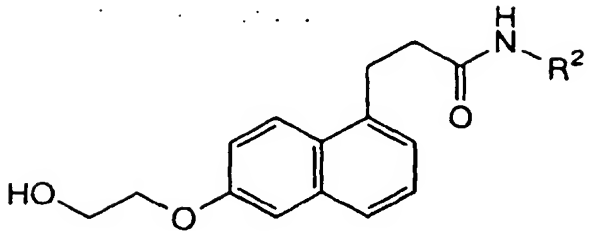

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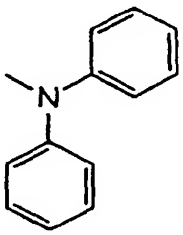
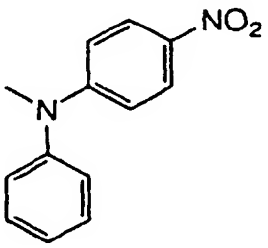
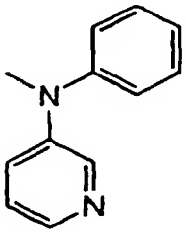
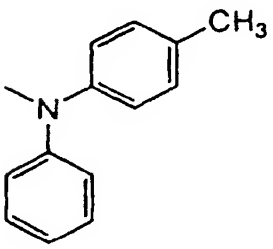
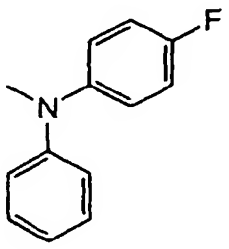
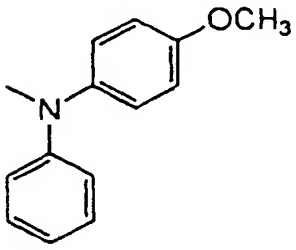
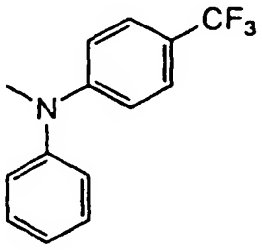

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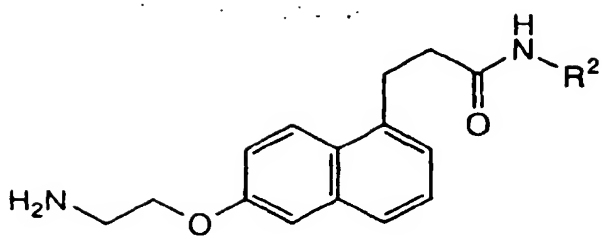

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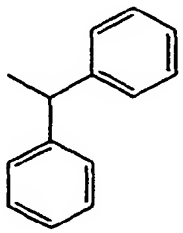
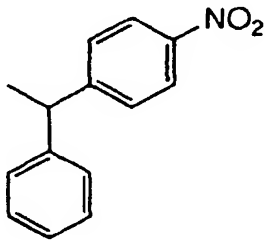
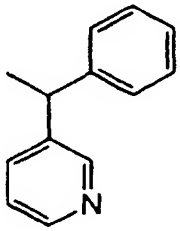
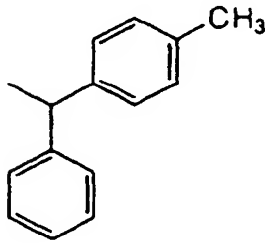
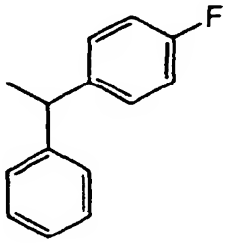
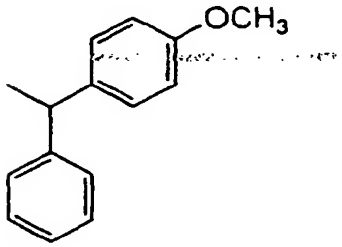
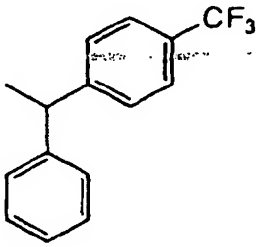

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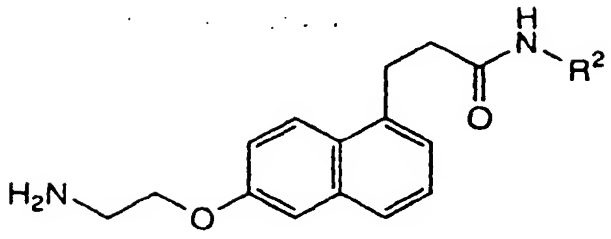

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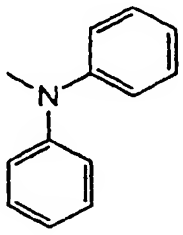
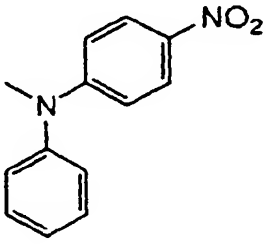
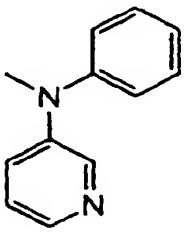
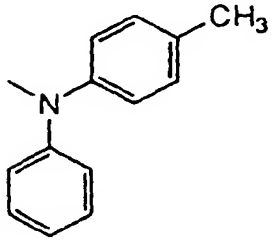
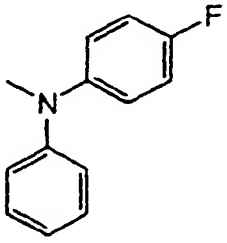
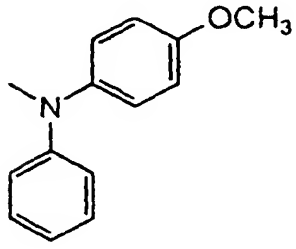
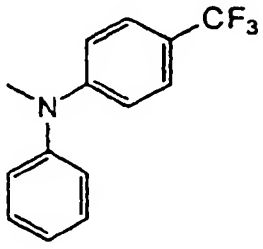

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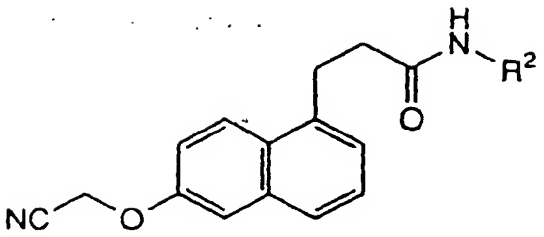

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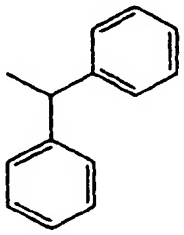
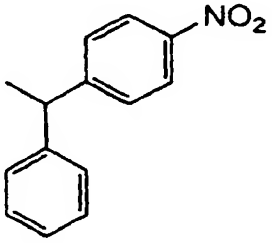
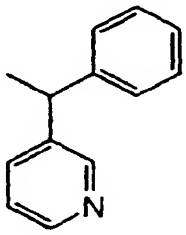
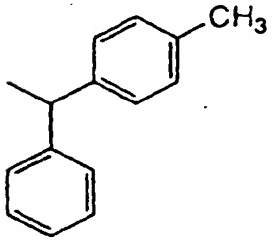
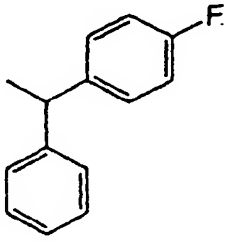
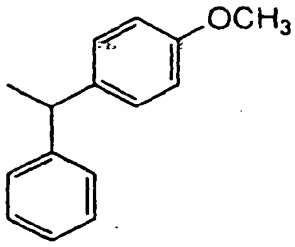
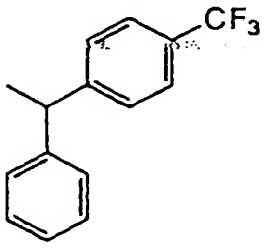

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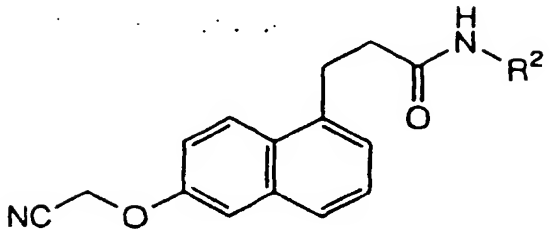

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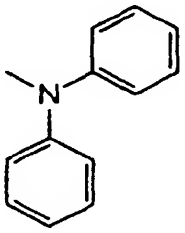
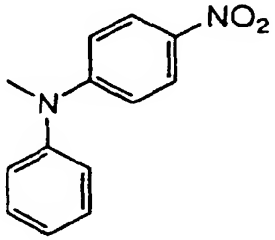
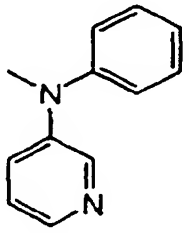
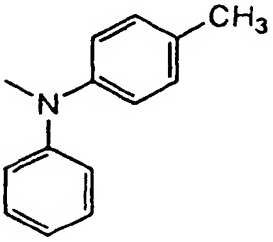
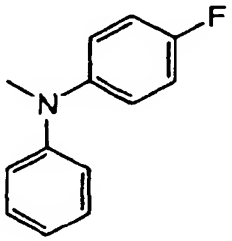
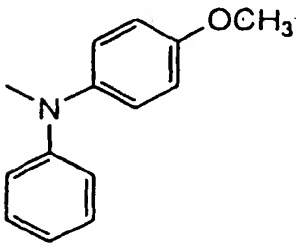
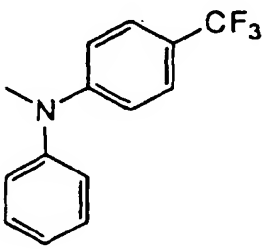

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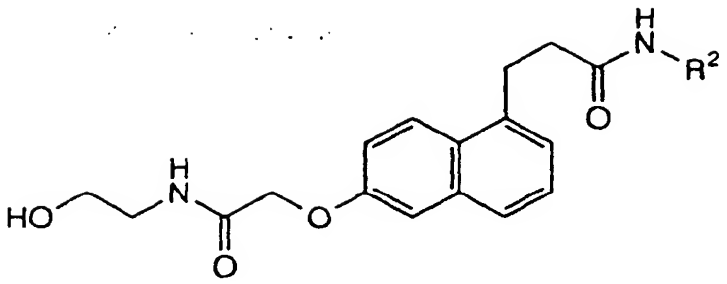

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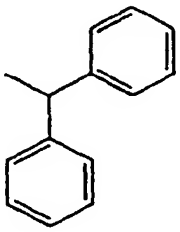
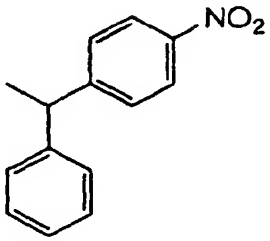
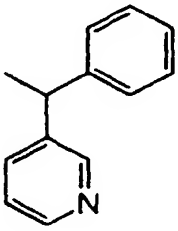
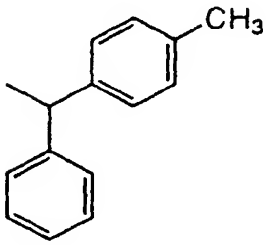
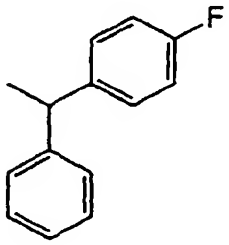
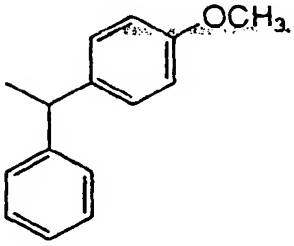
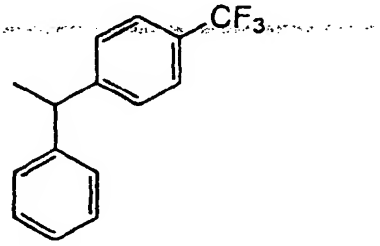

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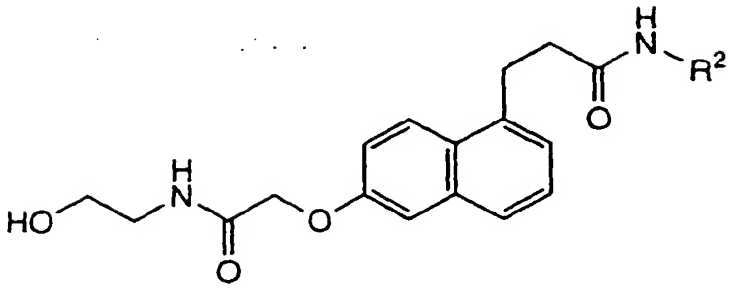

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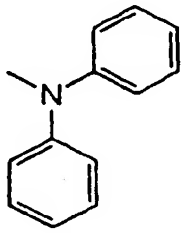
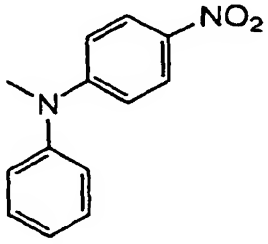
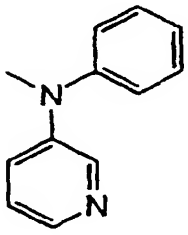
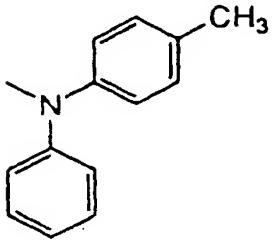
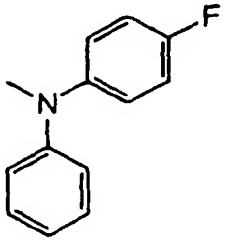
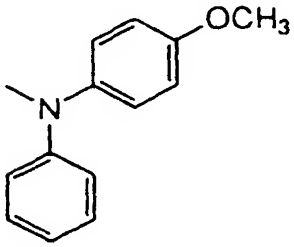
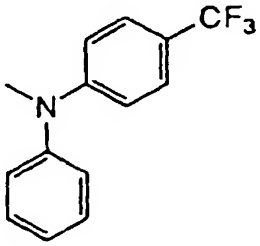

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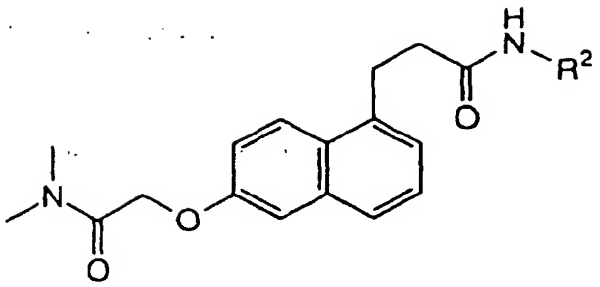

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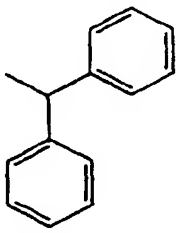
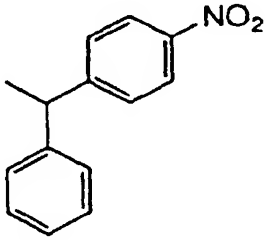
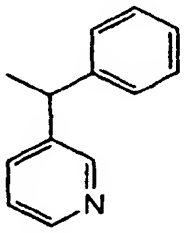
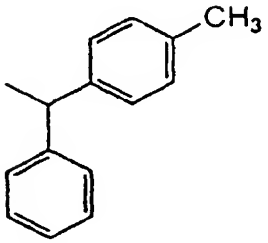
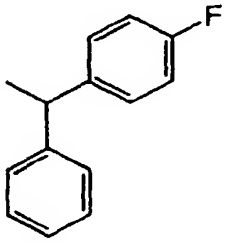
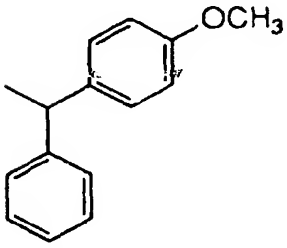
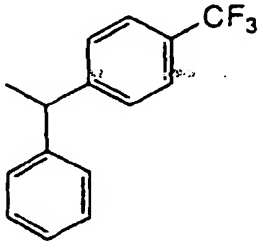

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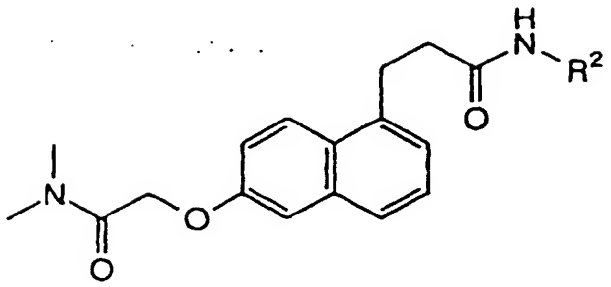

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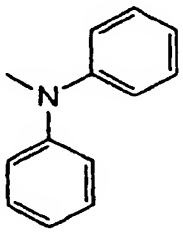 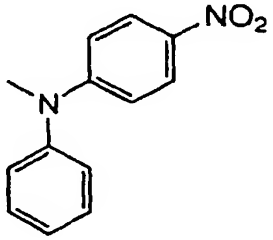 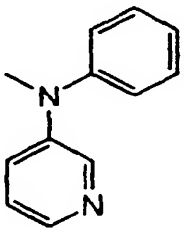
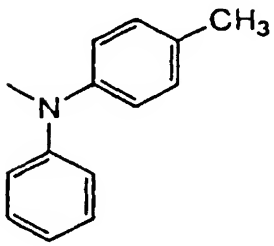 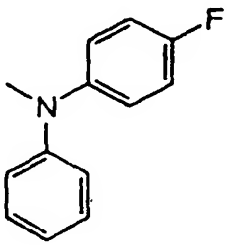
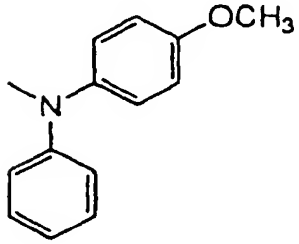 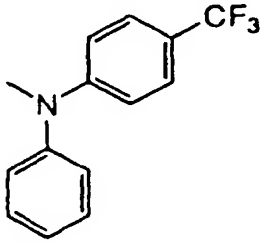

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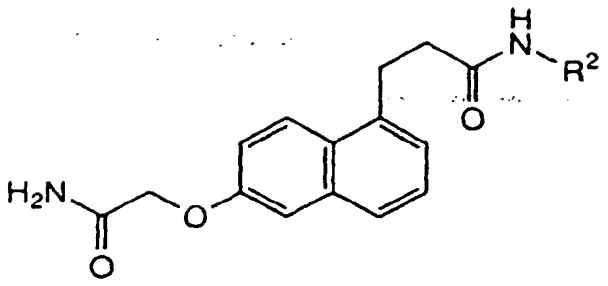

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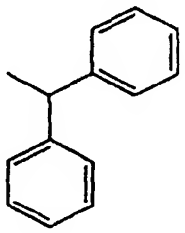
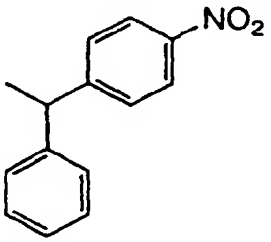
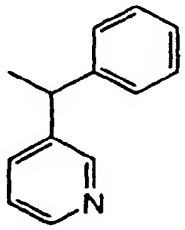
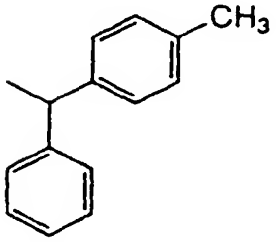
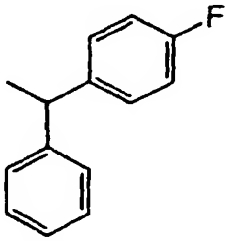
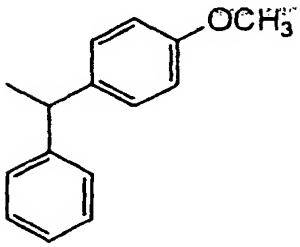
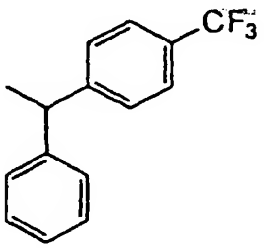

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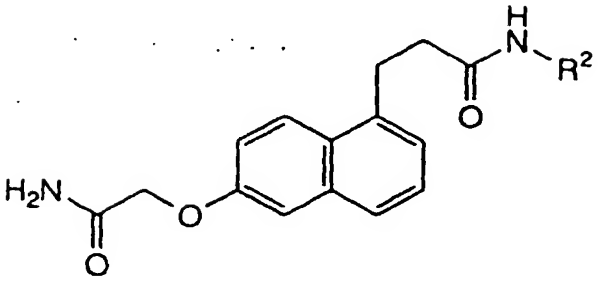

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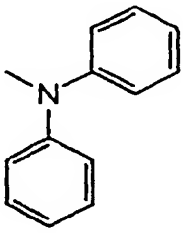
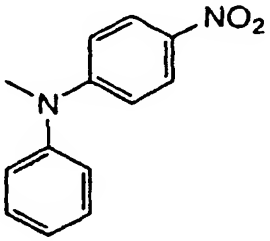
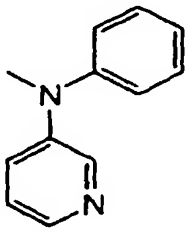
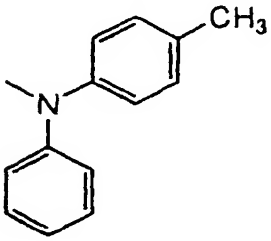
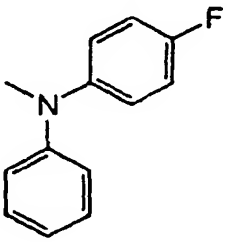
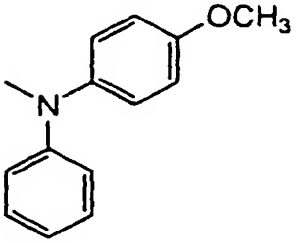
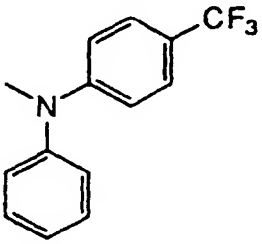

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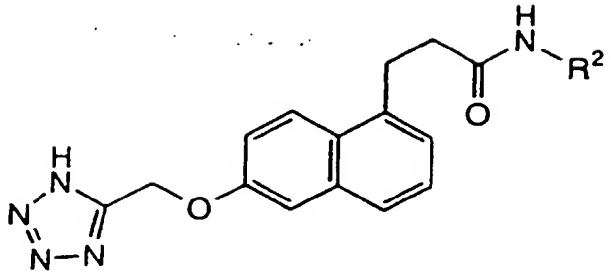

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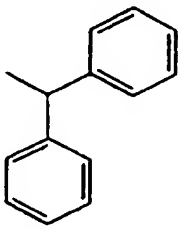
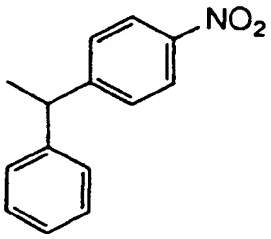
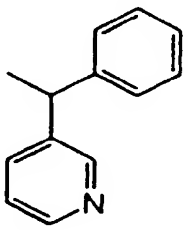
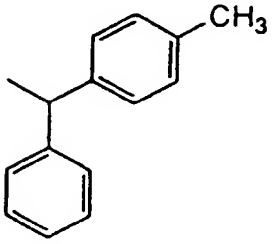
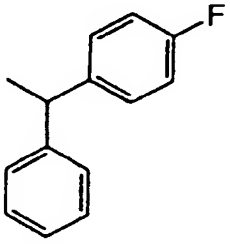
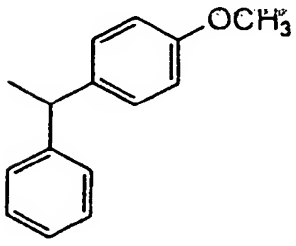
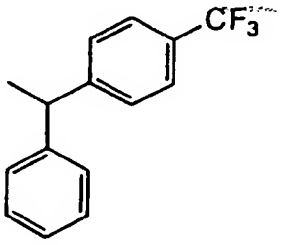

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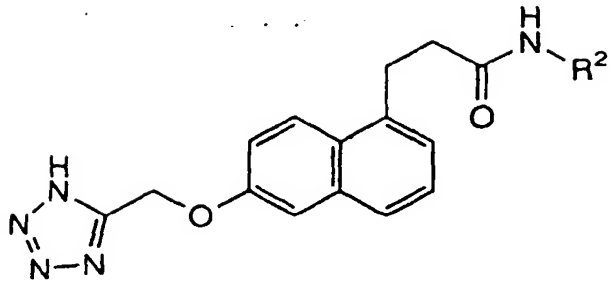

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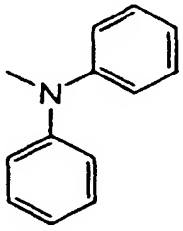
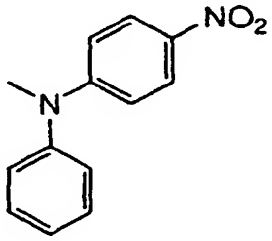
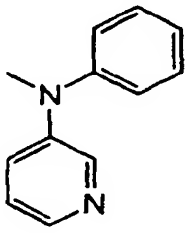
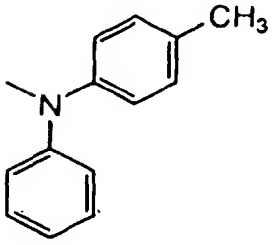
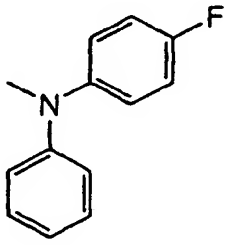
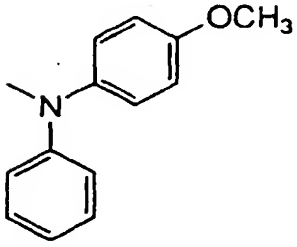
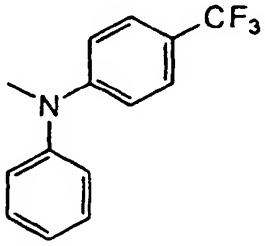

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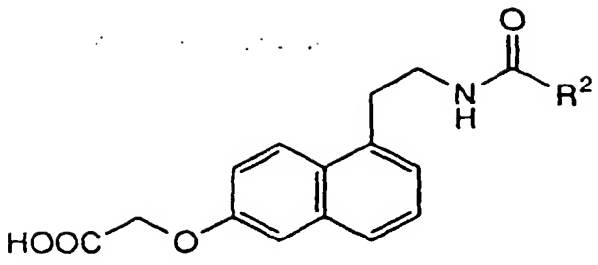

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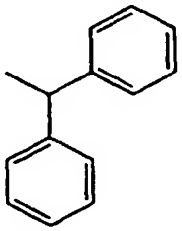
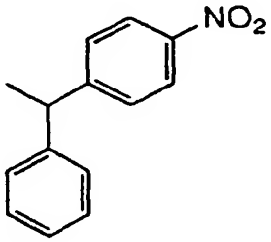
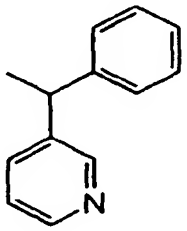
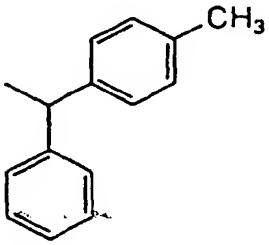
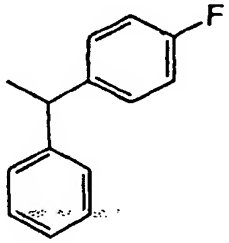
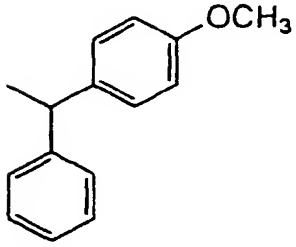
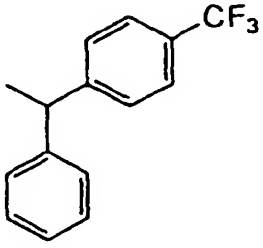

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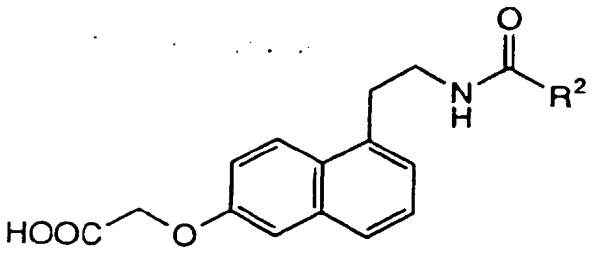

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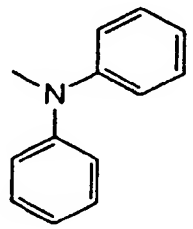
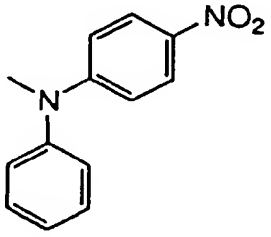
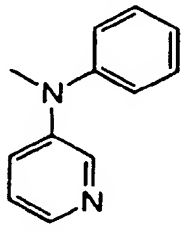
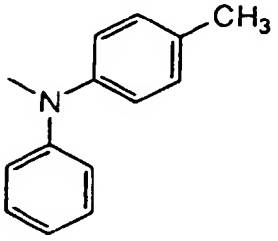
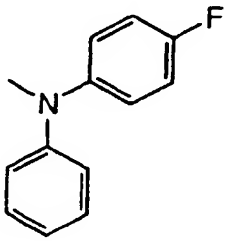
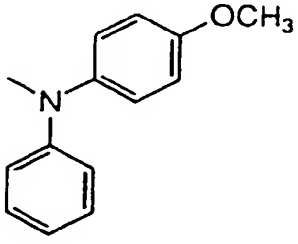
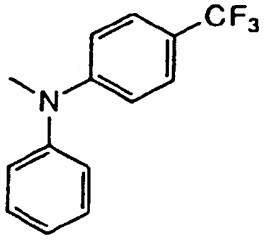
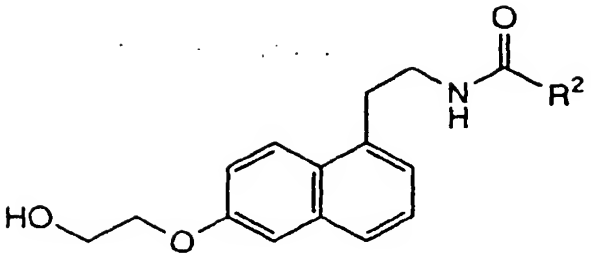
  
 
 

Table 10



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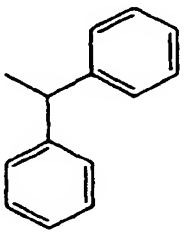
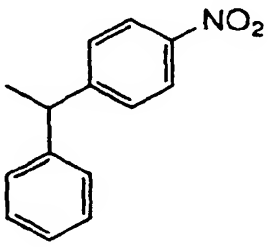
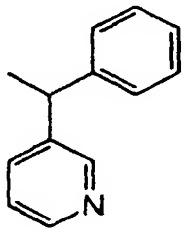
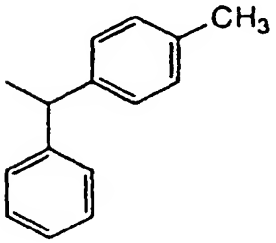
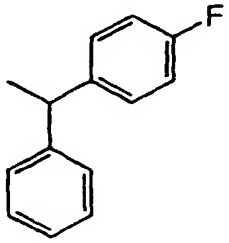
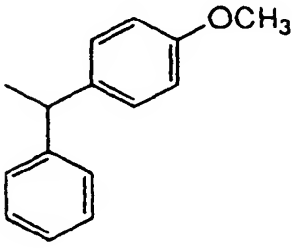
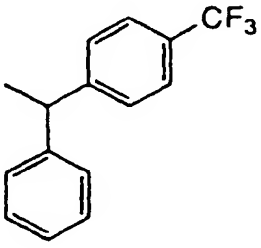

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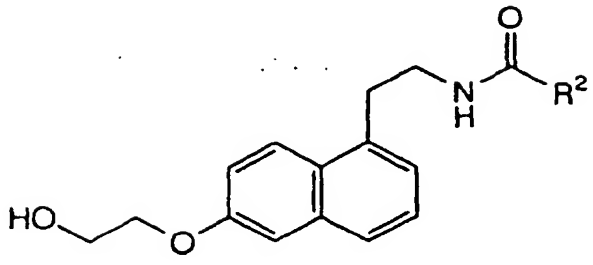

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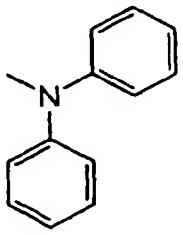
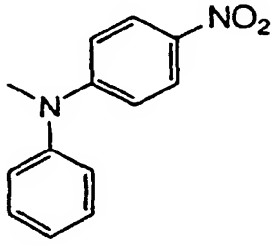
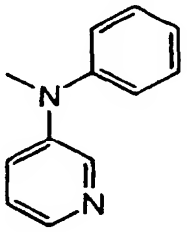
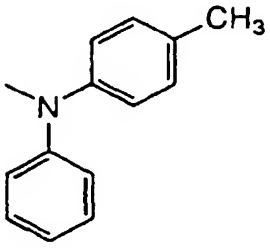
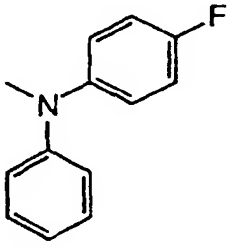
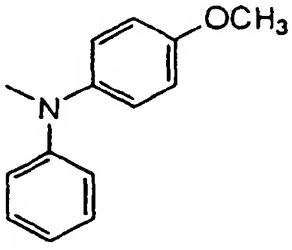
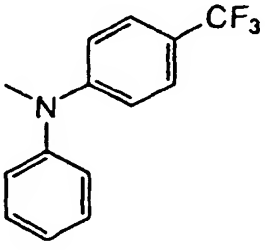

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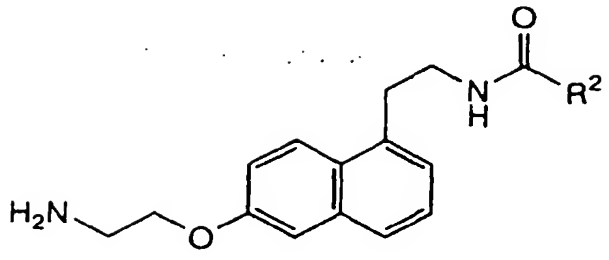

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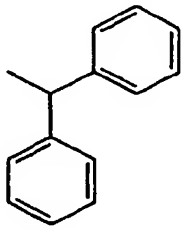
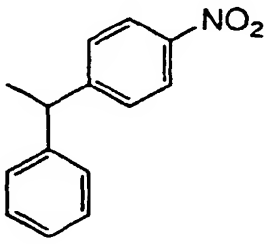
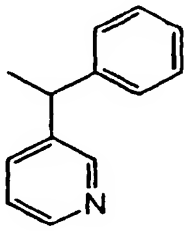
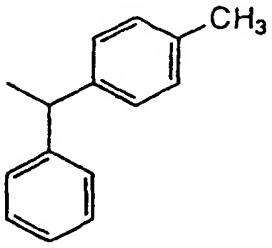
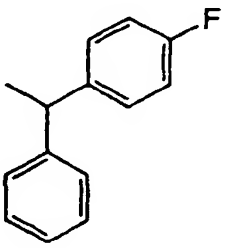
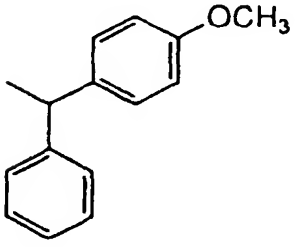
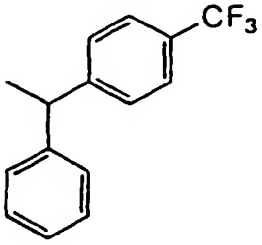

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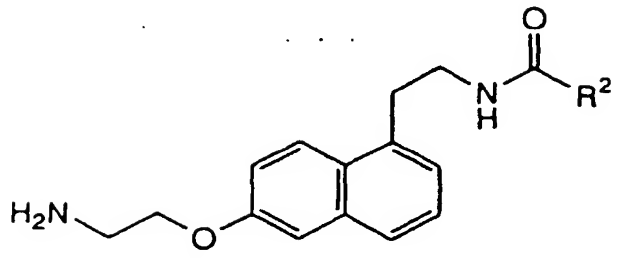

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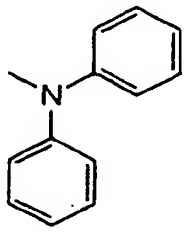
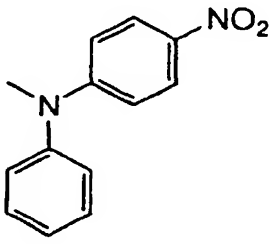
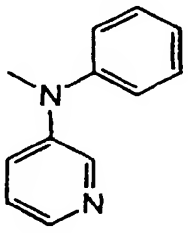
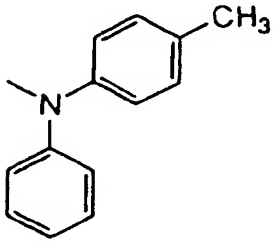
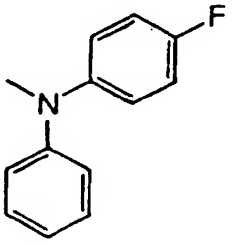
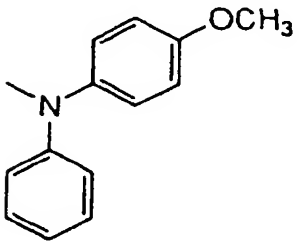
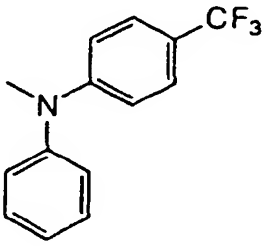

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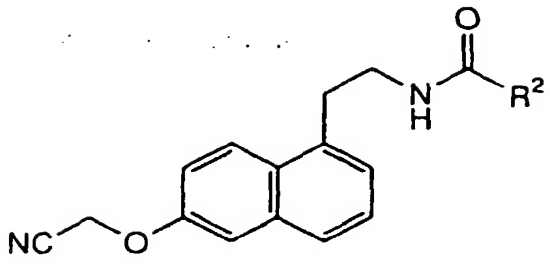

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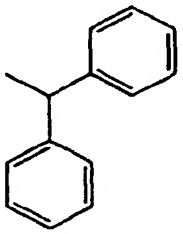
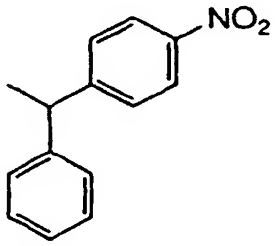
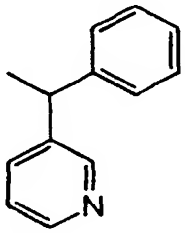
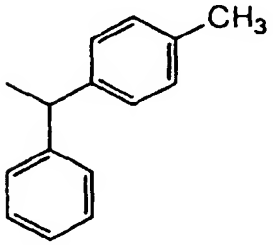
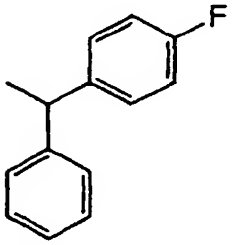
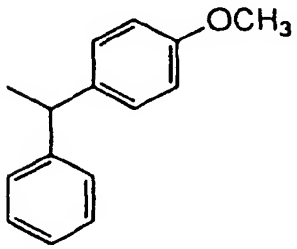
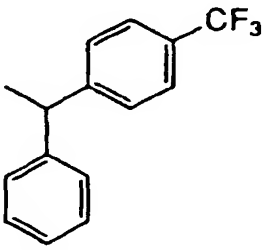

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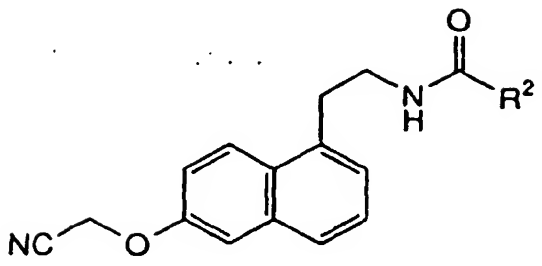

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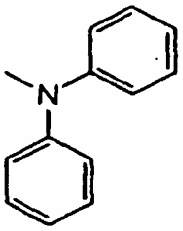
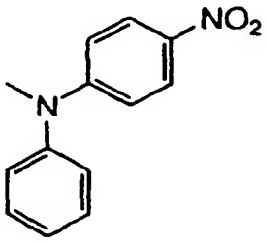
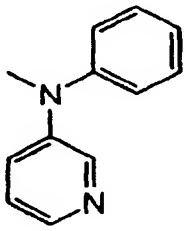
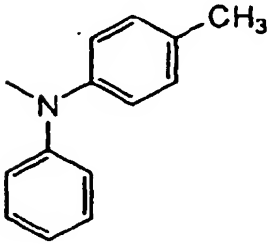
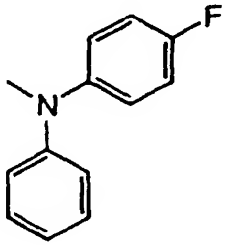
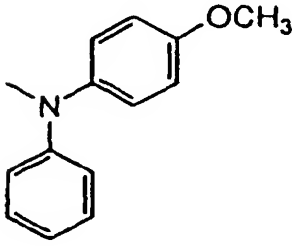
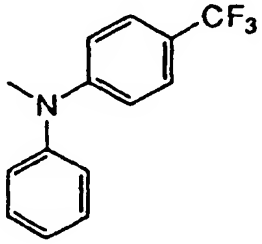

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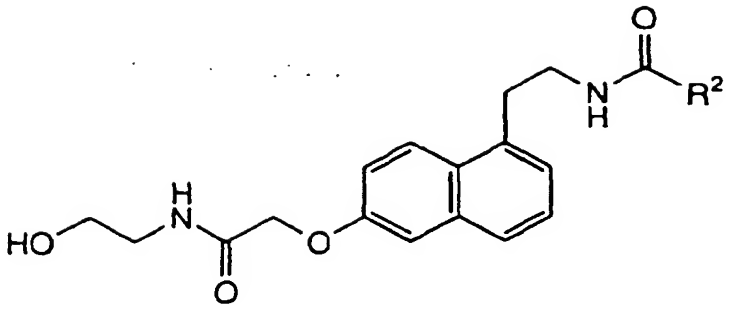

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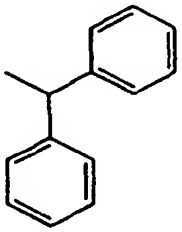
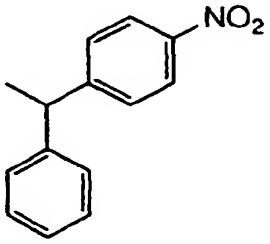
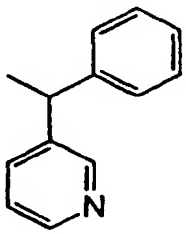
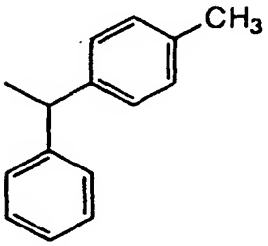
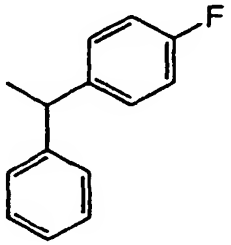
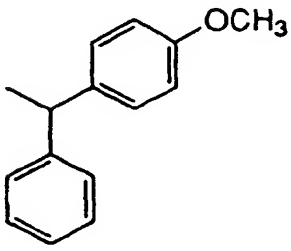
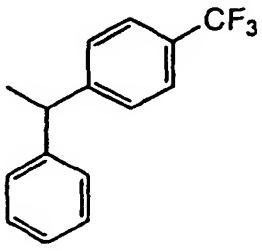

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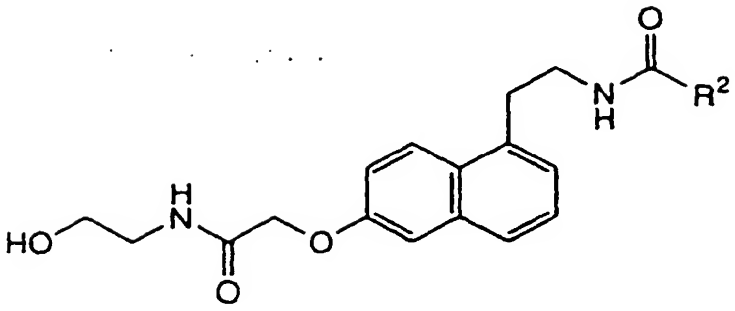

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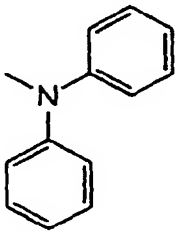
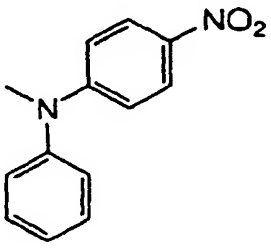
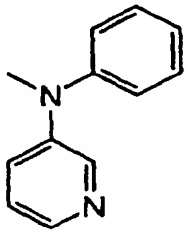
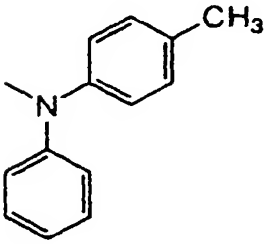
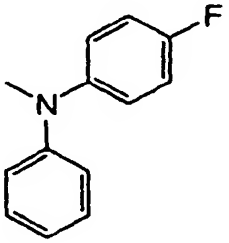
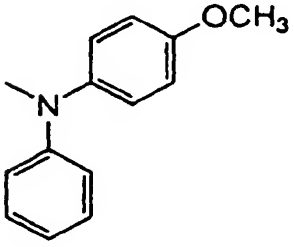
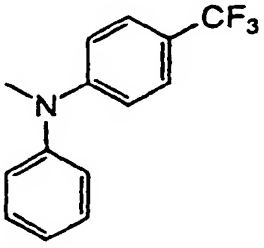

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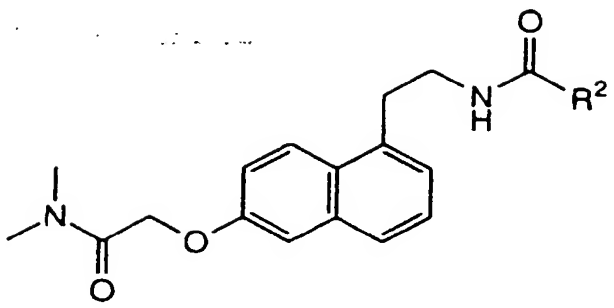

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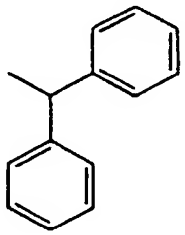
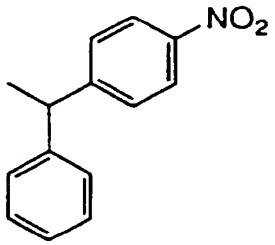
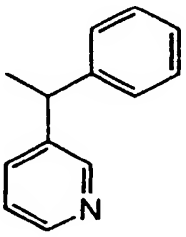
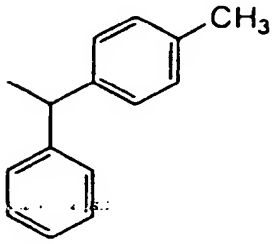
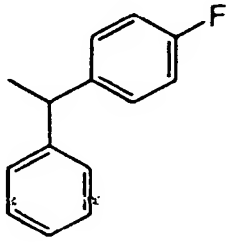
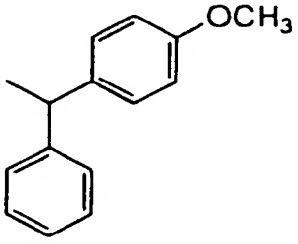
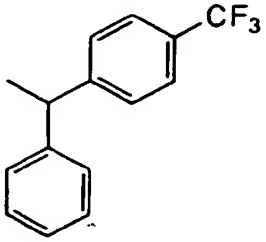

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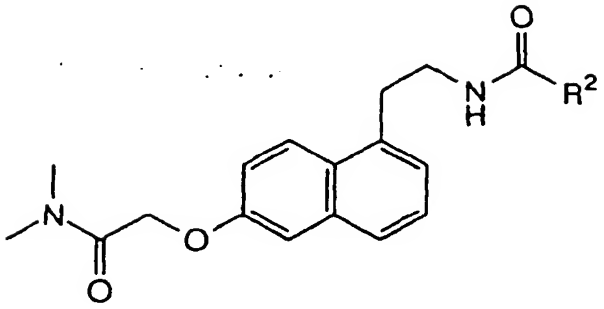

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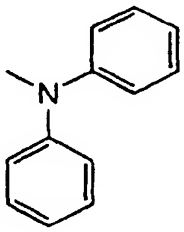
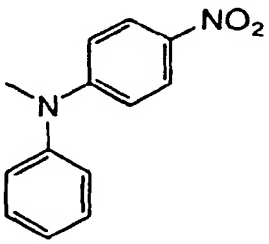
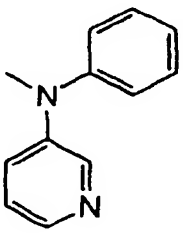
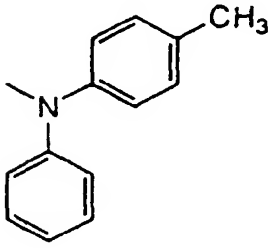
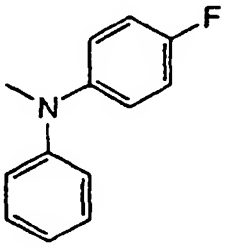
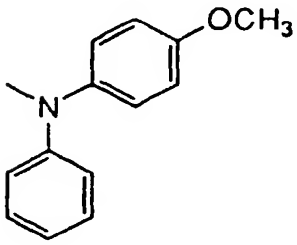
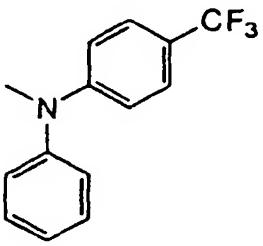

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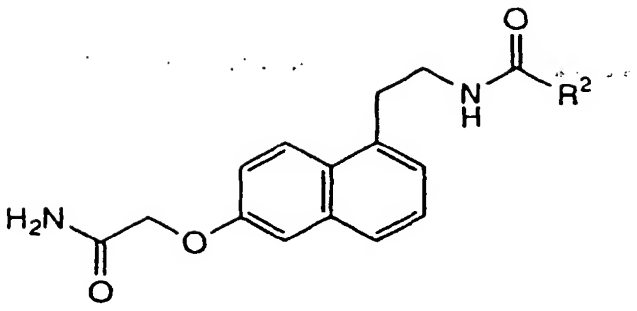

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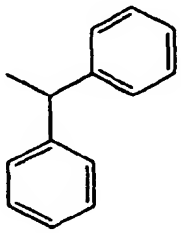
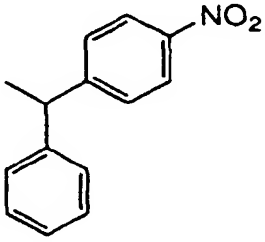
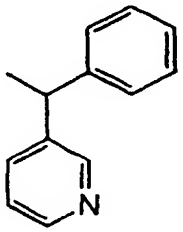
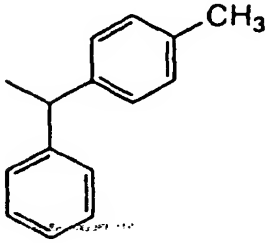
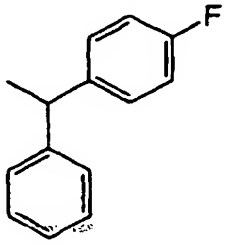
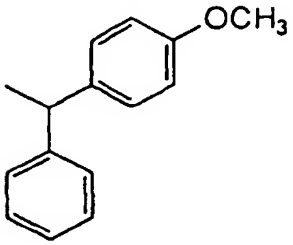
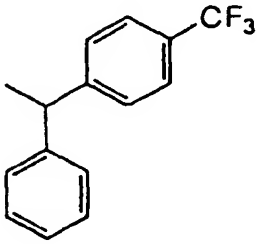

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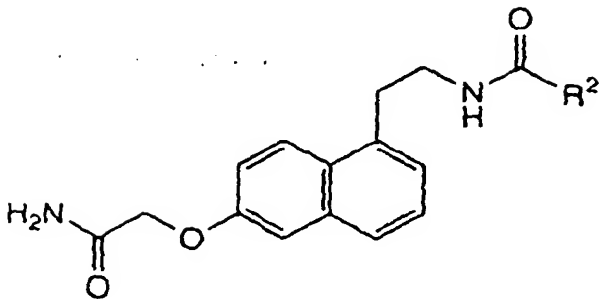

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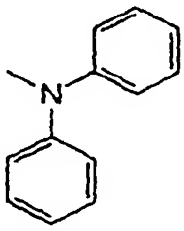
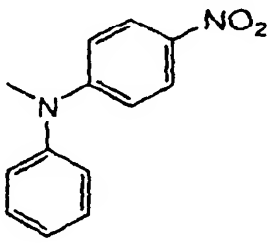
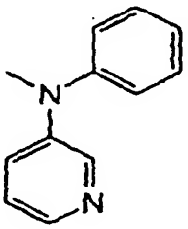
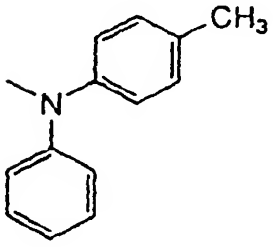
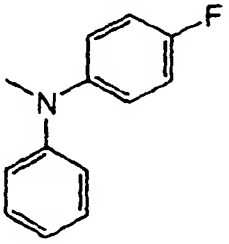
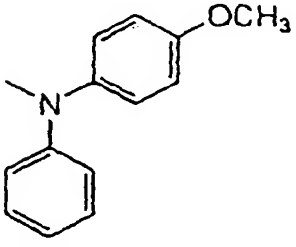
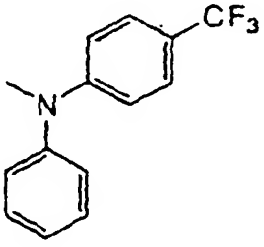

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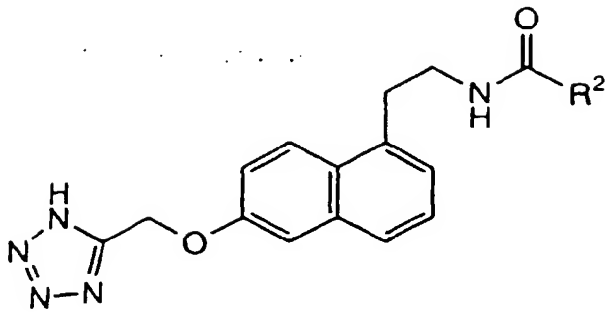

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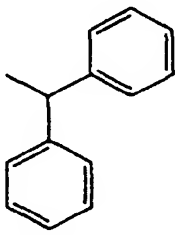
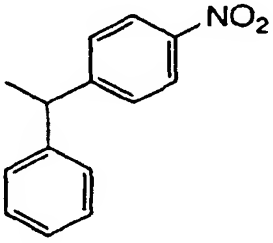
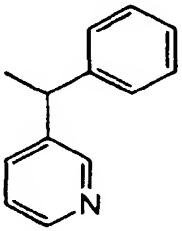
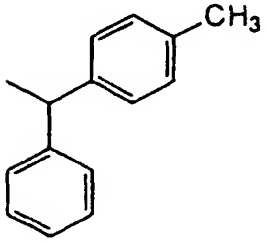
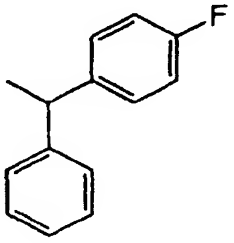
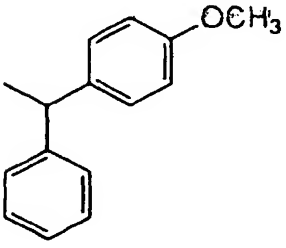
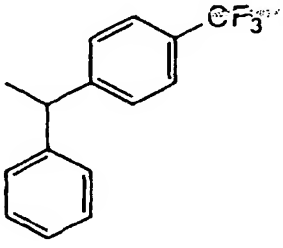

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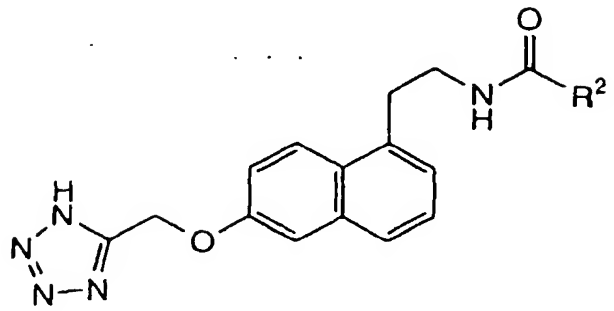

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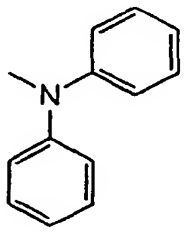
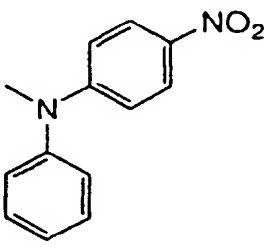
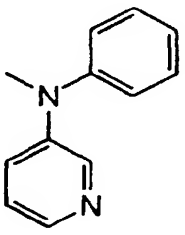
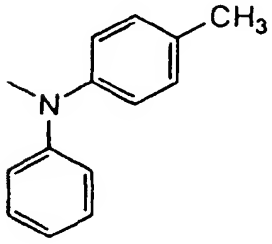
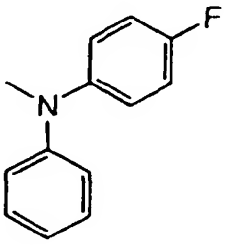
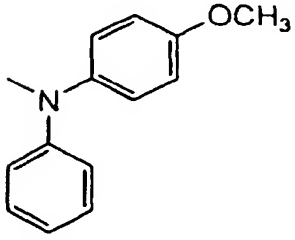
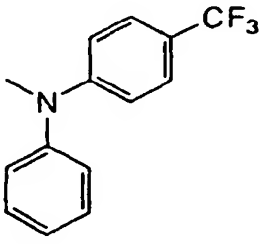

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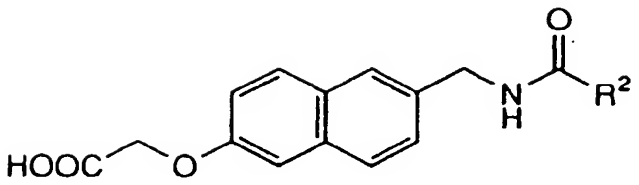

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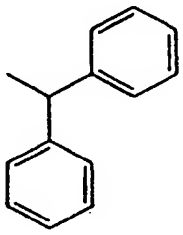
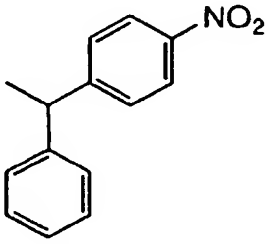
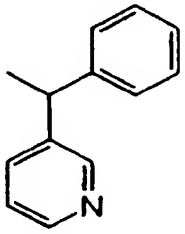
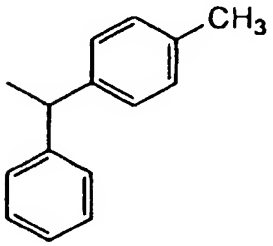
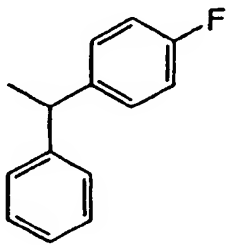
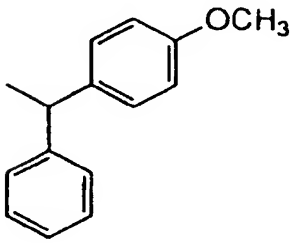
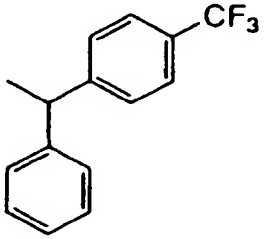

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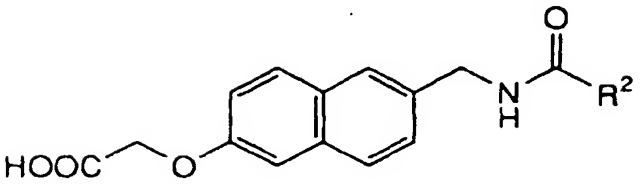

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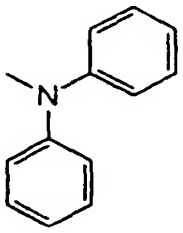
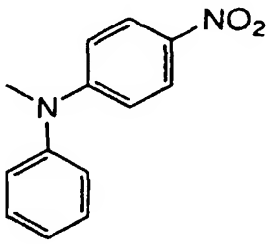
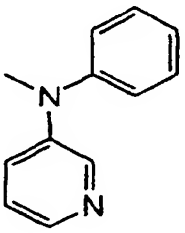
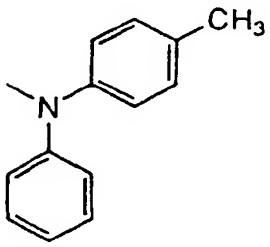
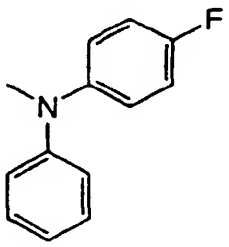
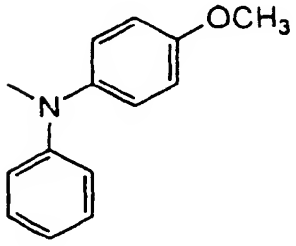
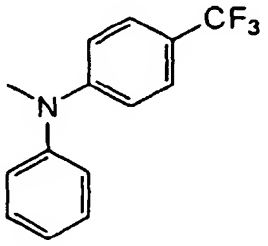

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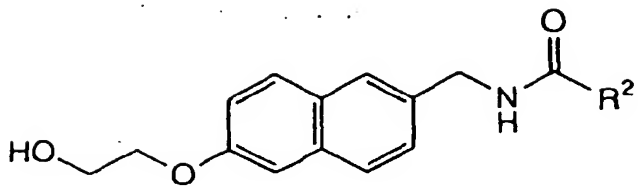

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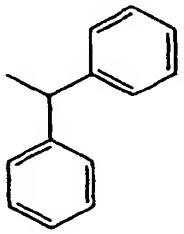
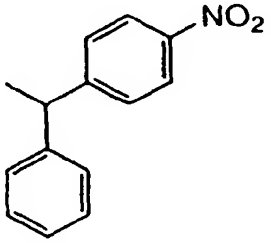
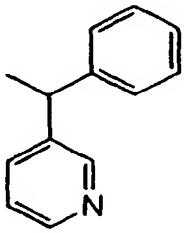
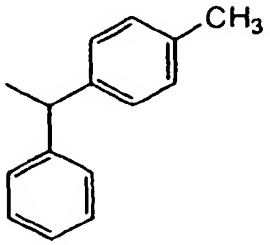
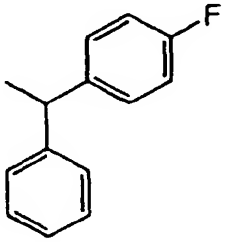
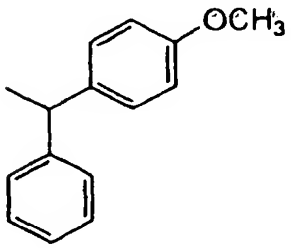
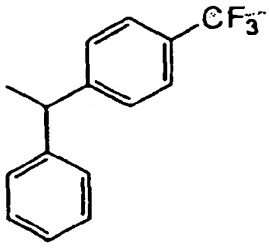

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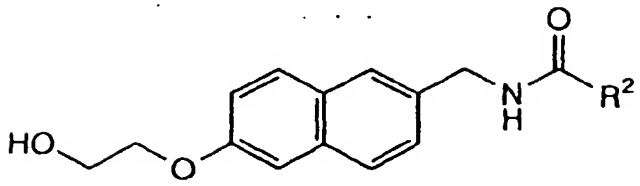

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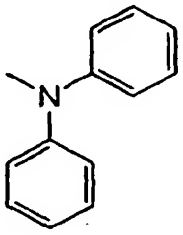
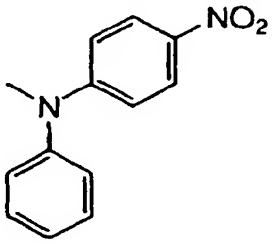
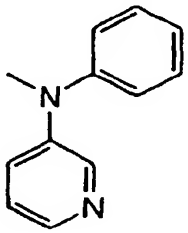
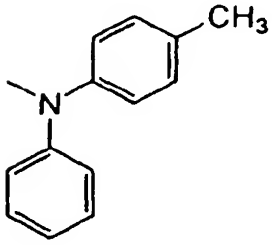
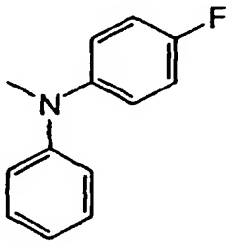
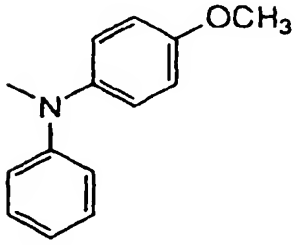
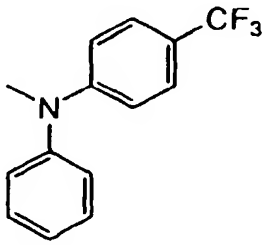

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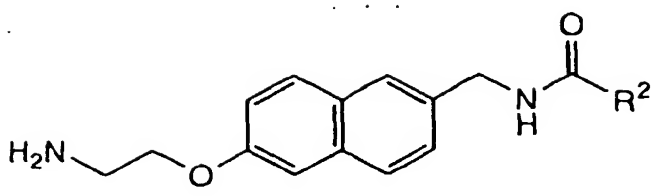

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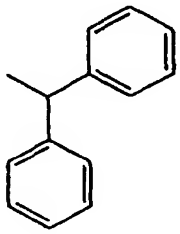
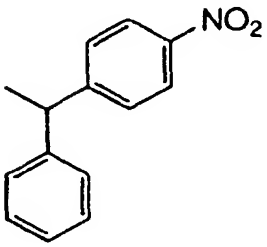
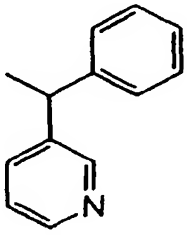
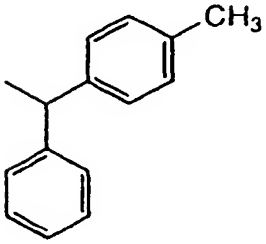
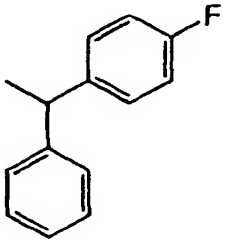
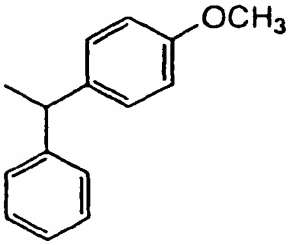
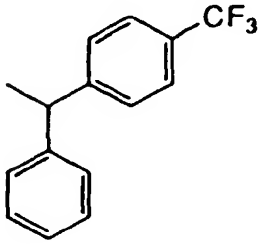

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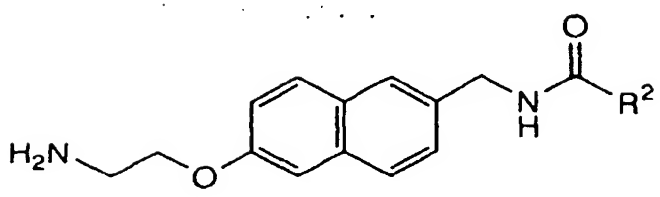

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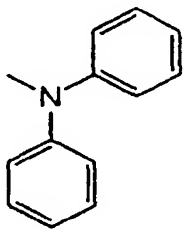
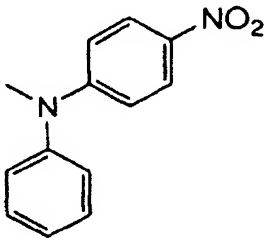
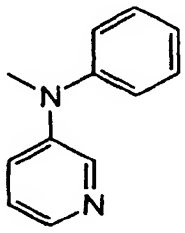
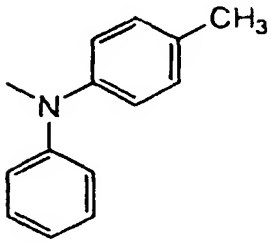
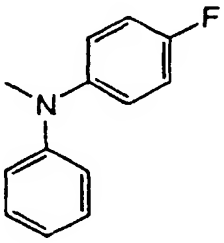
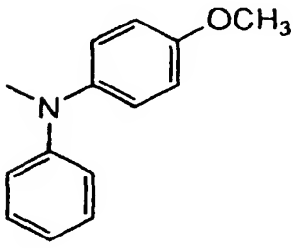
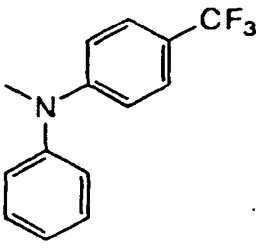

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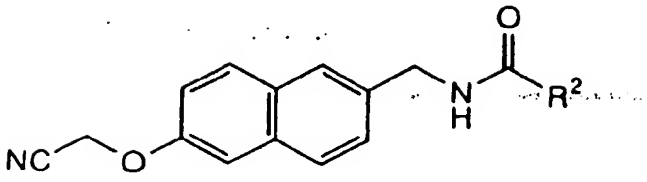

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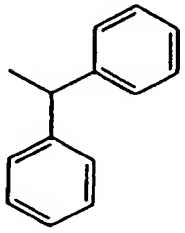
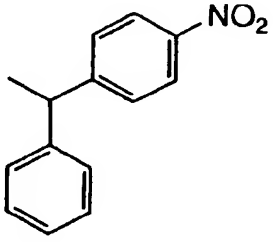
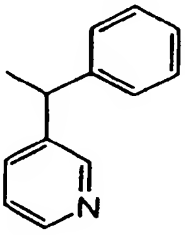
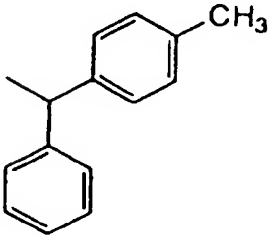
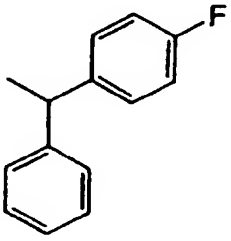
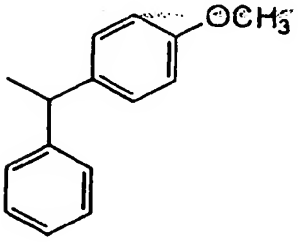
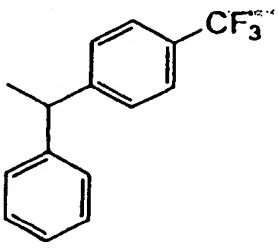

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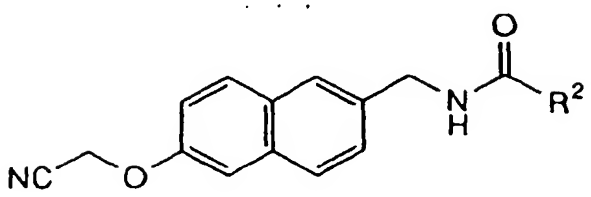

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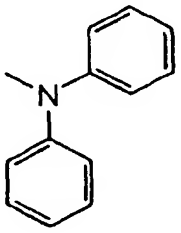
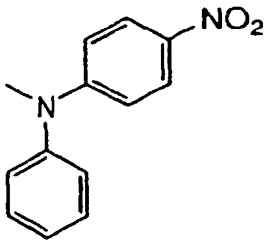
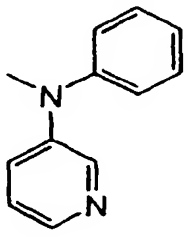
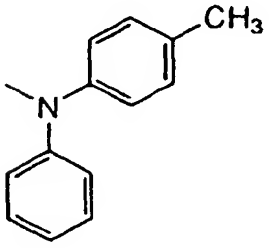
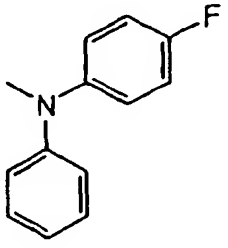
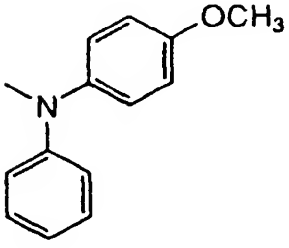
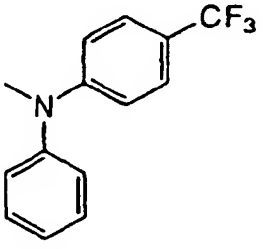

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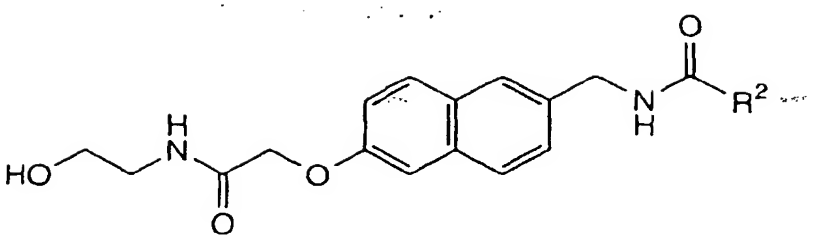

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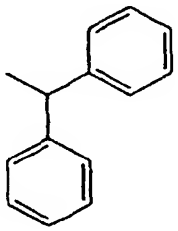
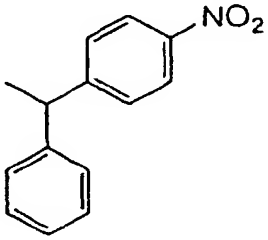
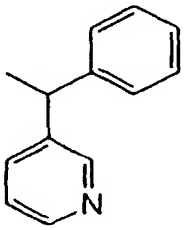
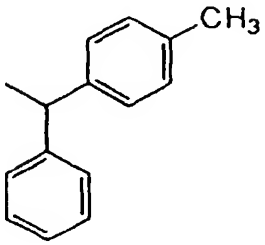
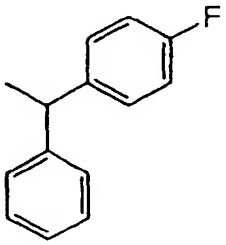
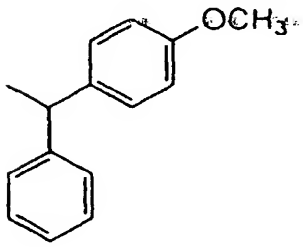
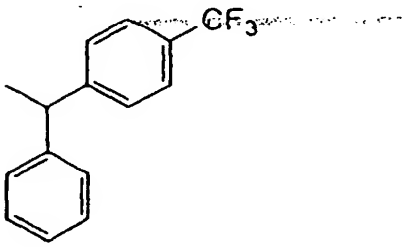

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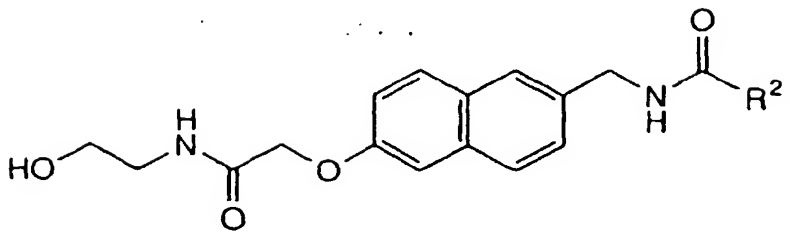

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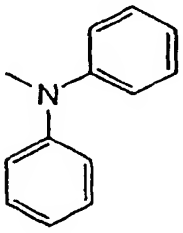
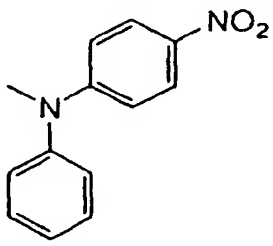
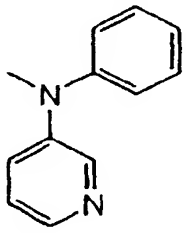
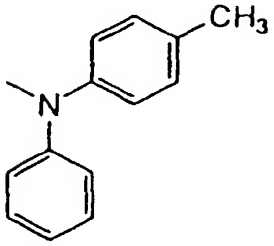
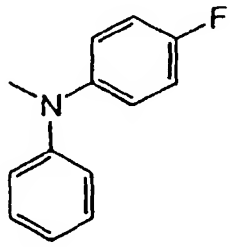
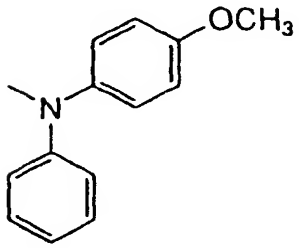
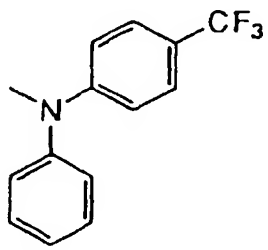

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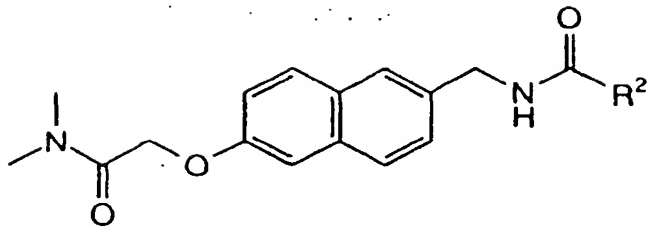

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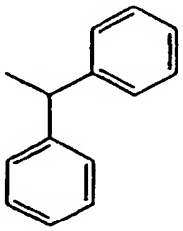
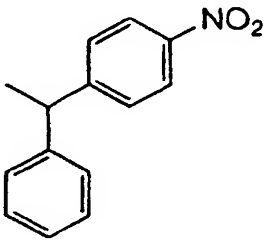
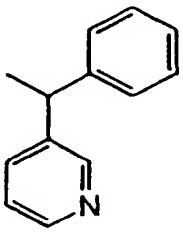
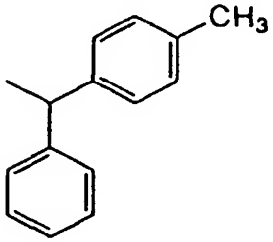
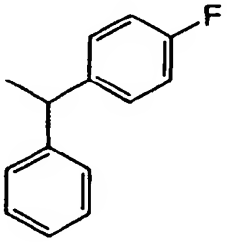
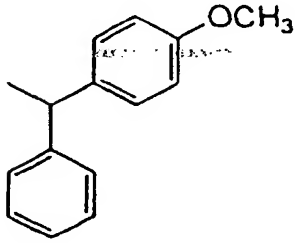
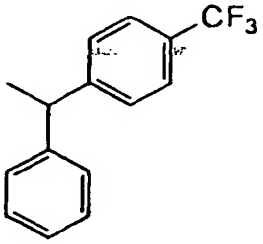

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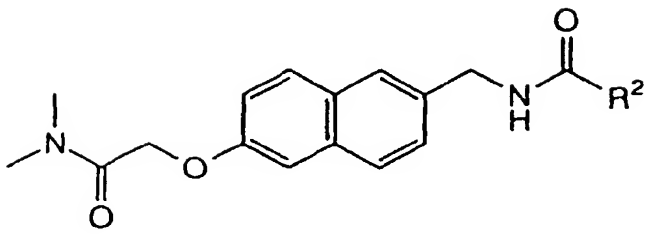

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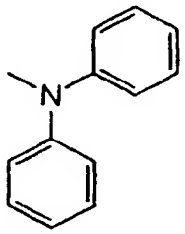
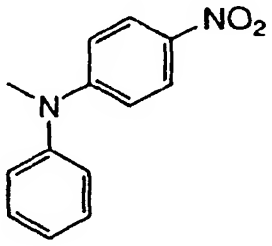
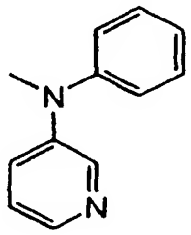
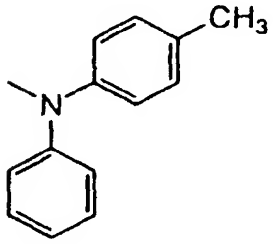
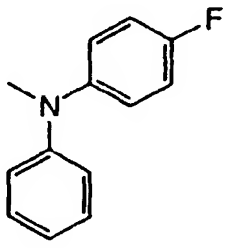
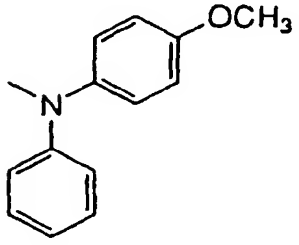
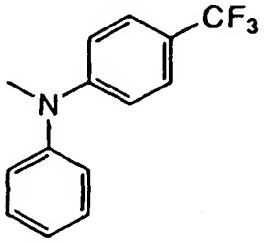

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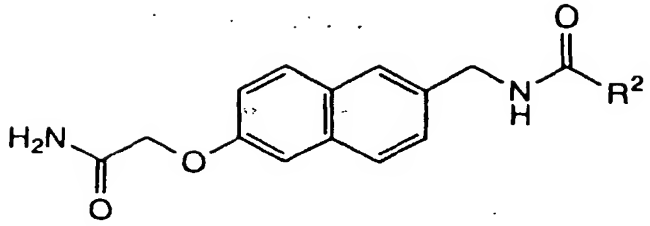

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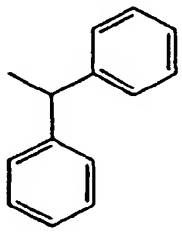
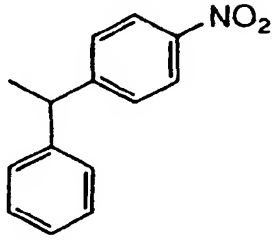
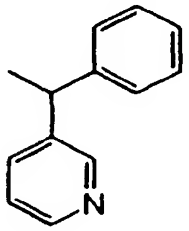
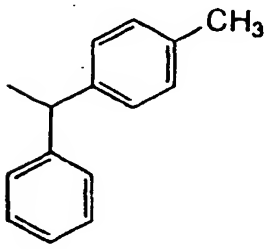
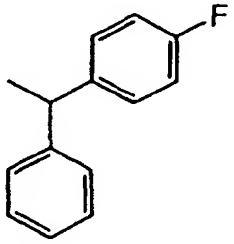
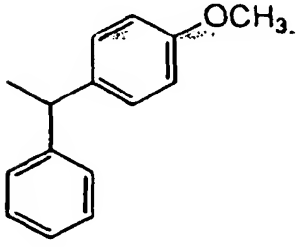
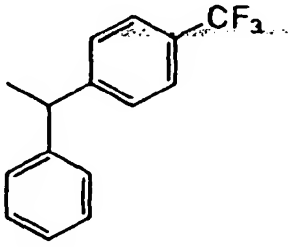

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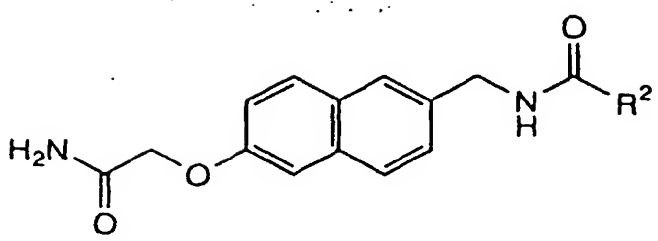

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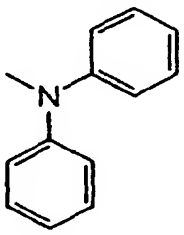
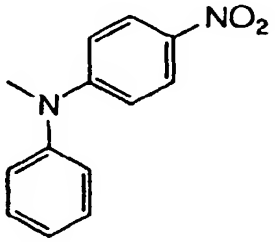
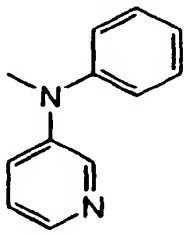
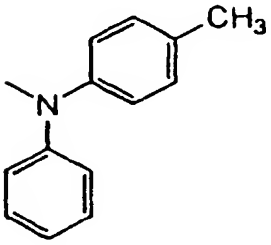
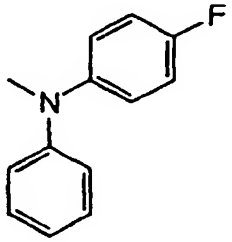
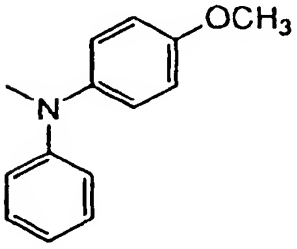
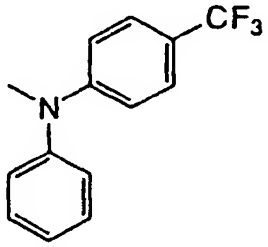

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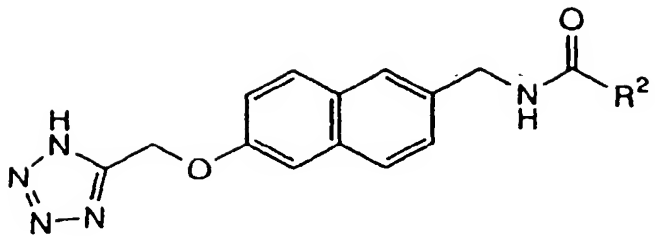

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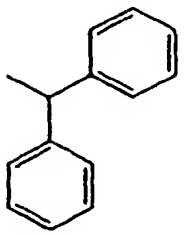
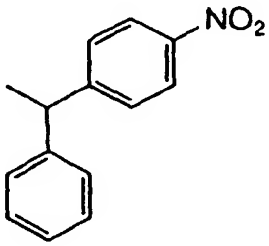
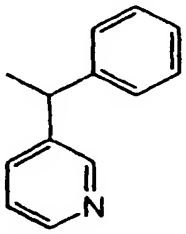
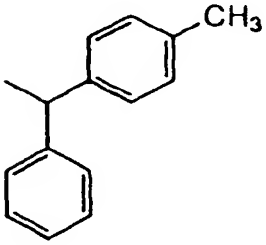
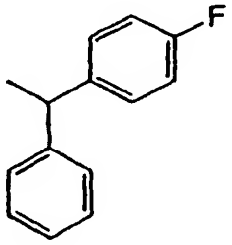
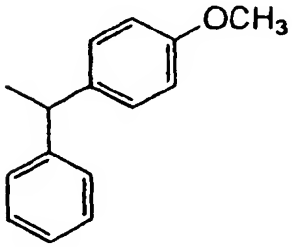
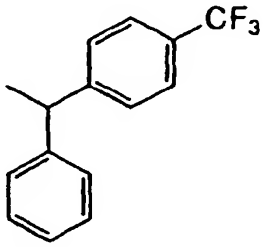

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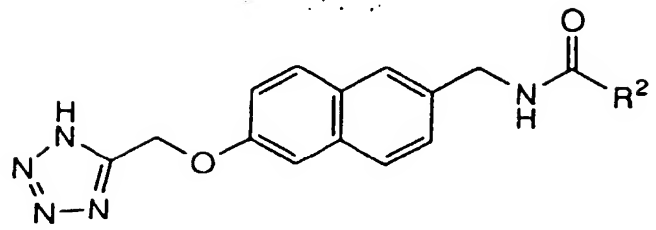

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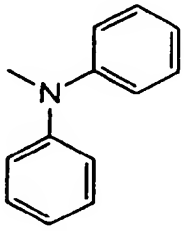
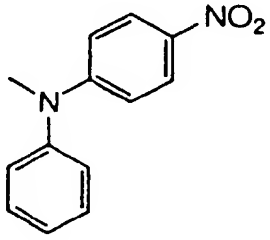
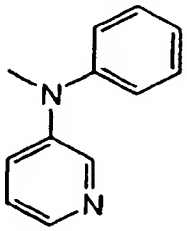
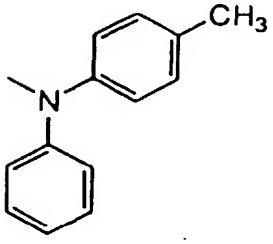
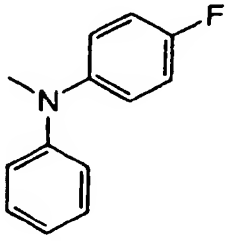
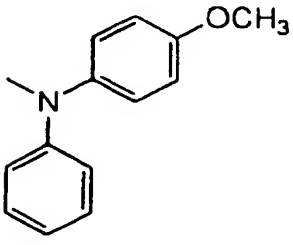
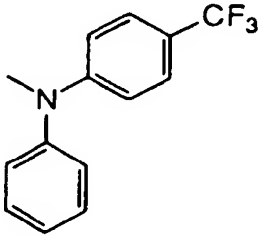

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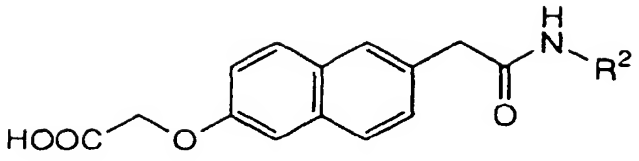

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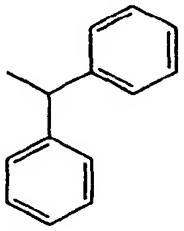
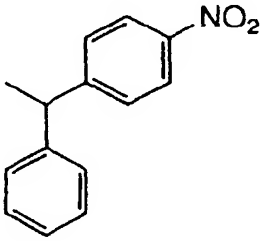
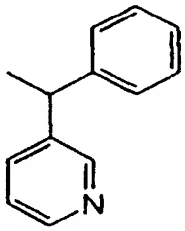
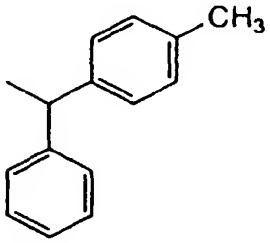
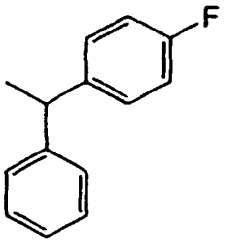
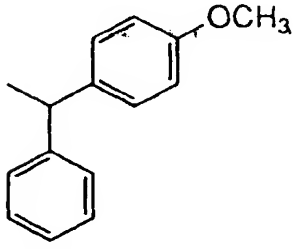
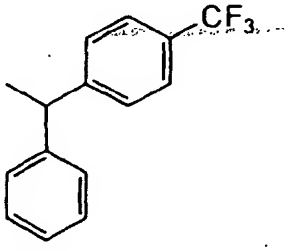

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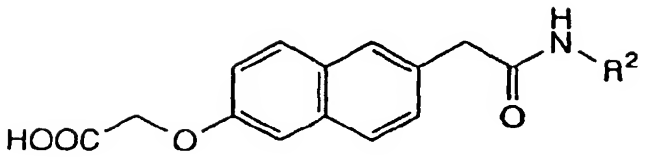

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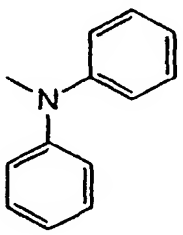
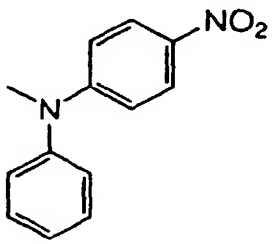
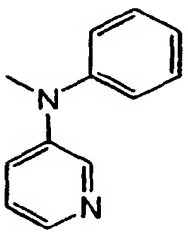
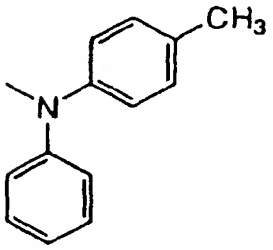
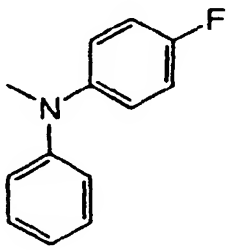
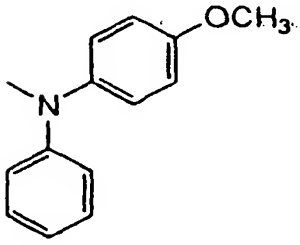
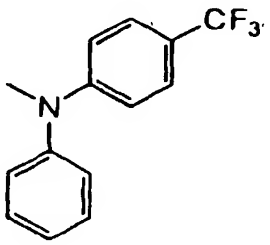

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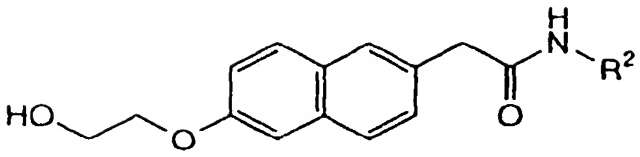

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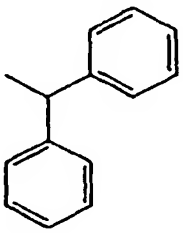
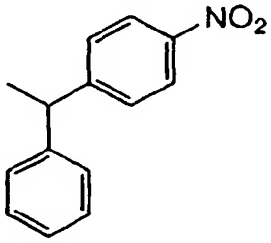
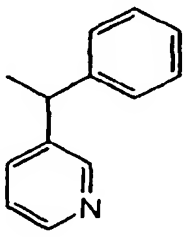
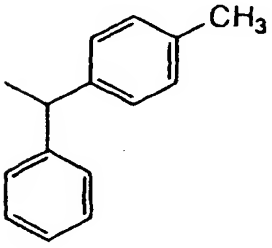
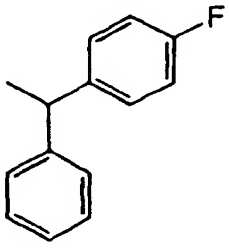
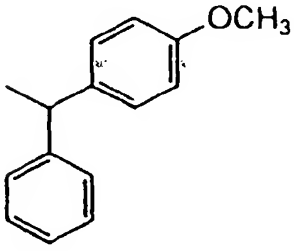
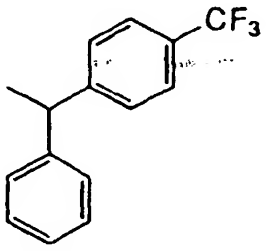

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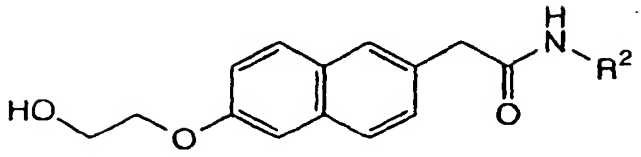

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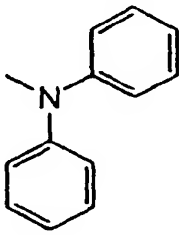
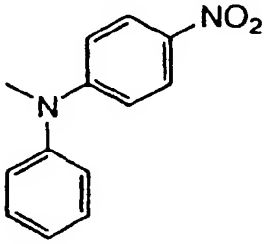
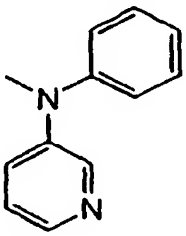
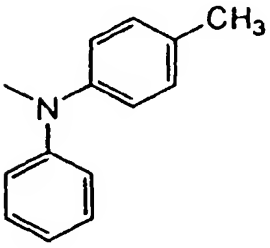
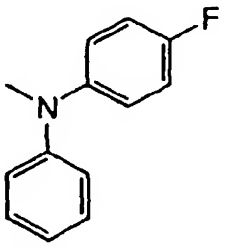
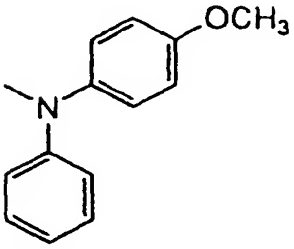
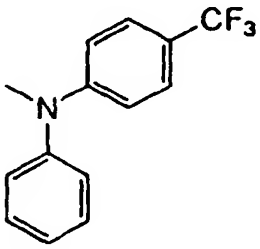

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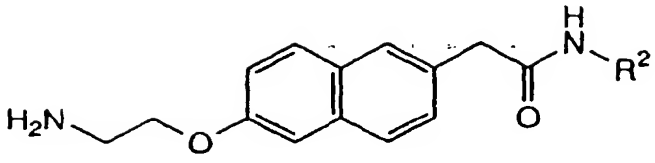

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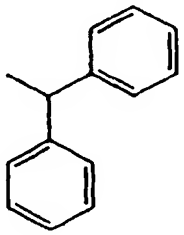
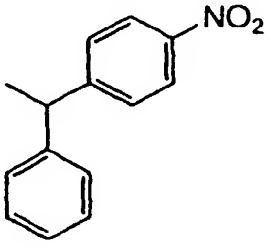
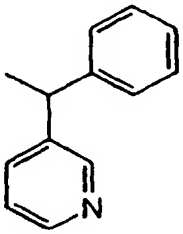
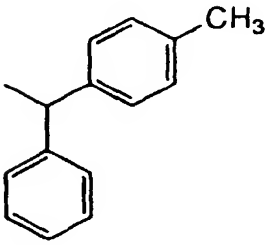
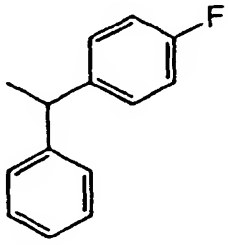
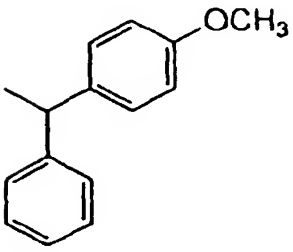
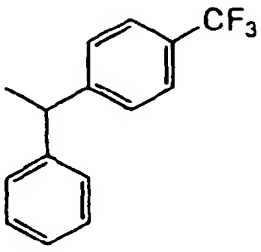

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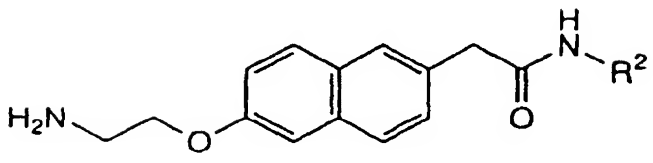

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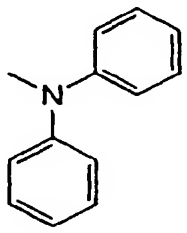
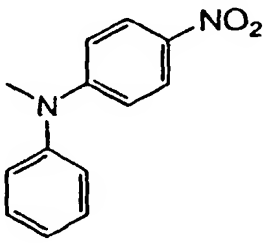
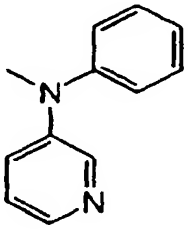
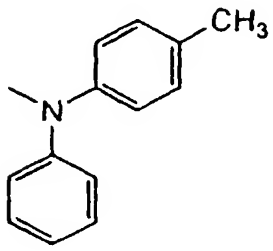
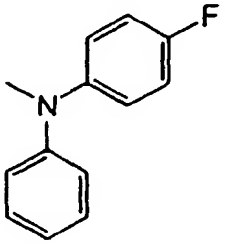
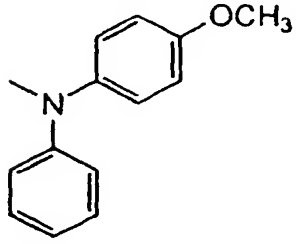
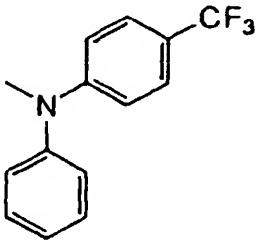

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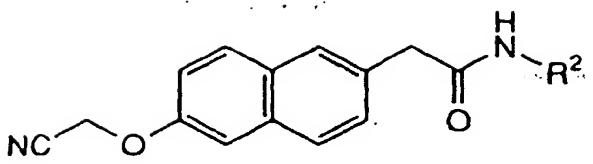

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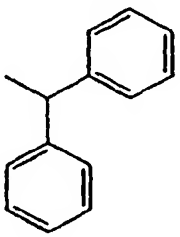
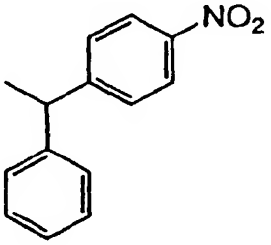
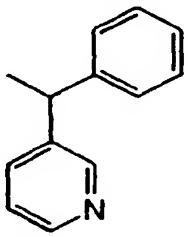
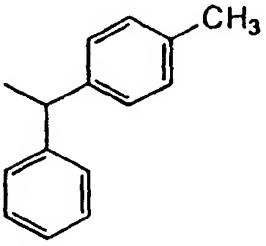
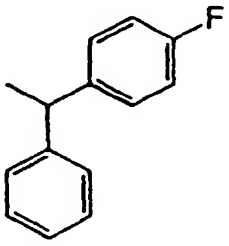
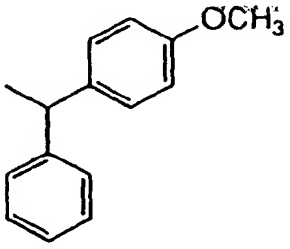
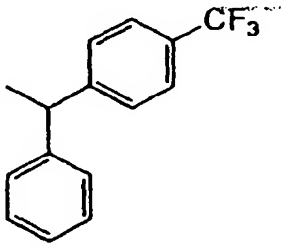

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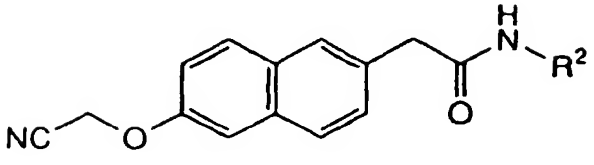

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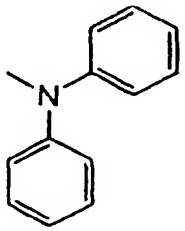
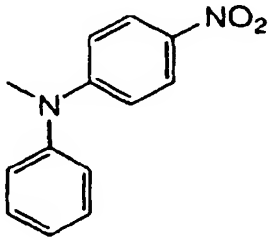
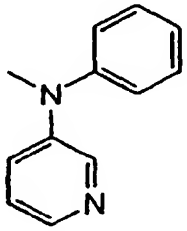
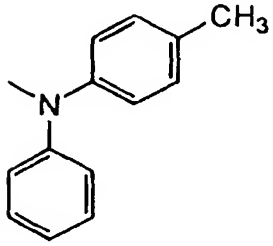
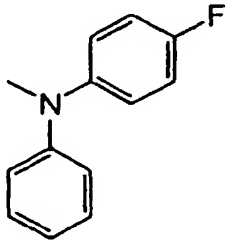
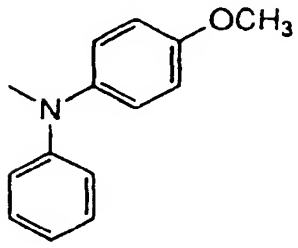
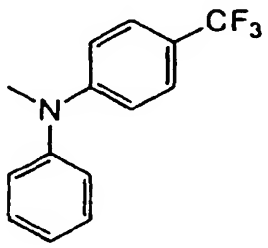

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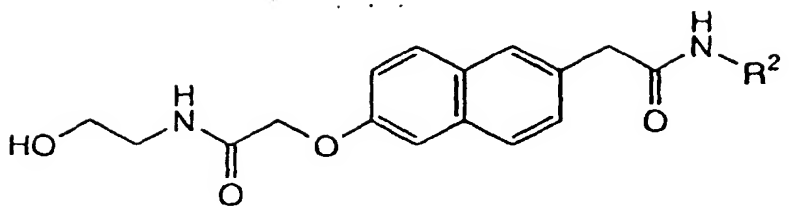

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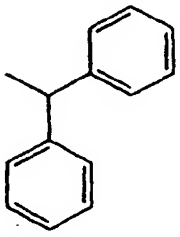
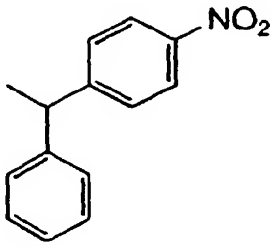
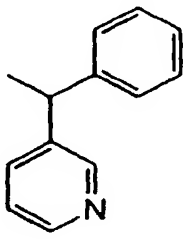
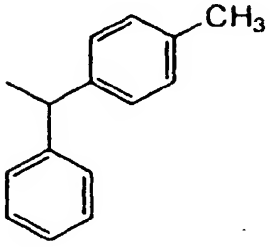
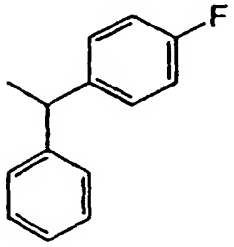
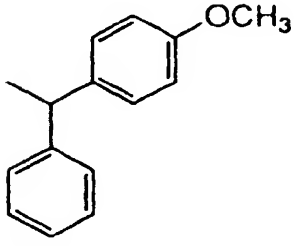
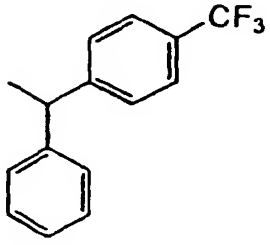

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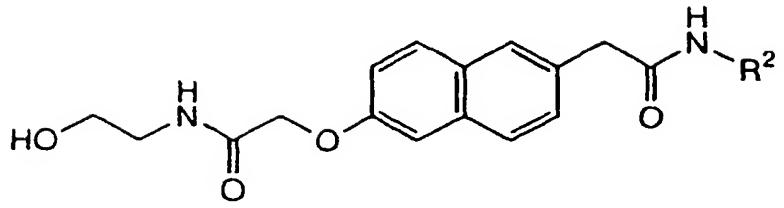

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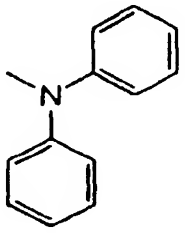
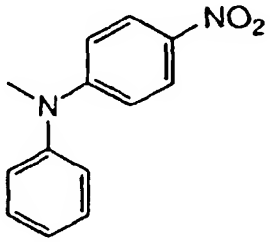
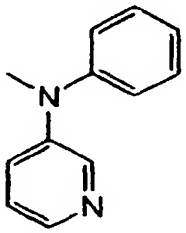
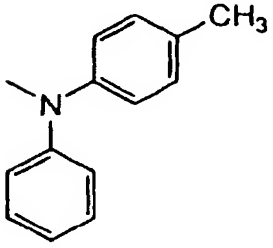
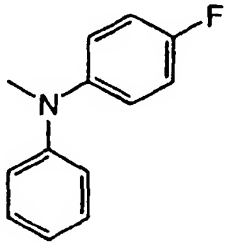
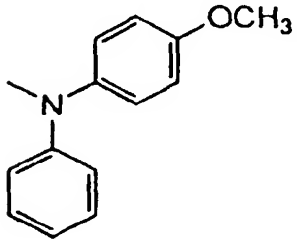
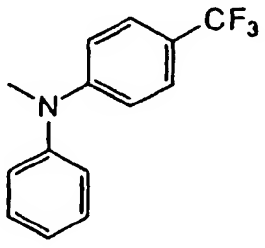

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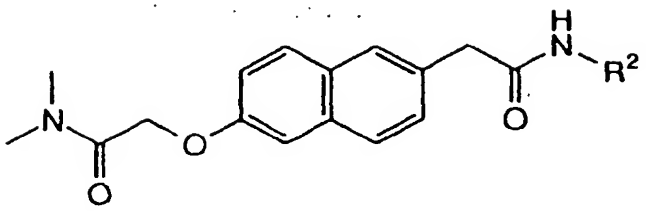

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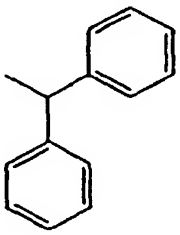
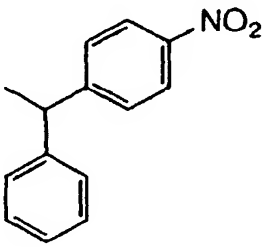
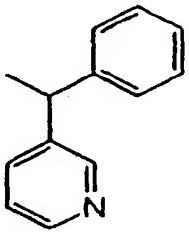
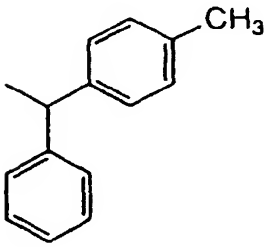
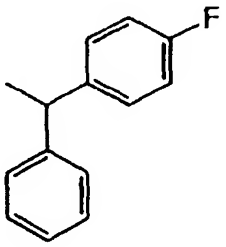
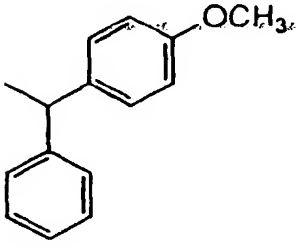
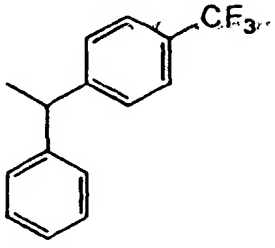

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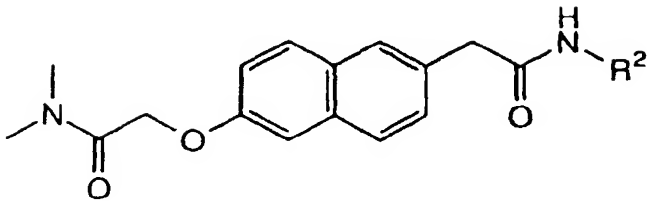

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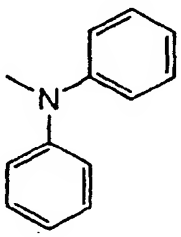
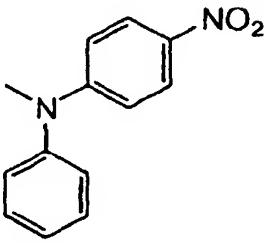
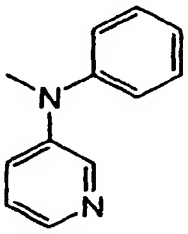
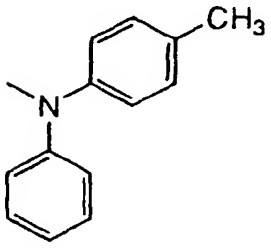
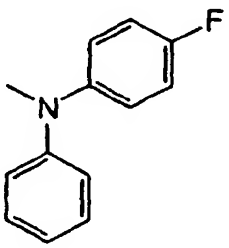
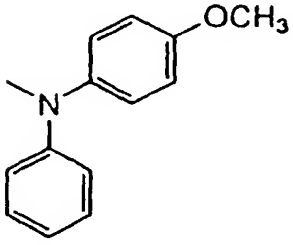
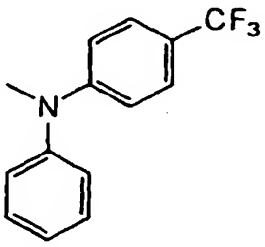

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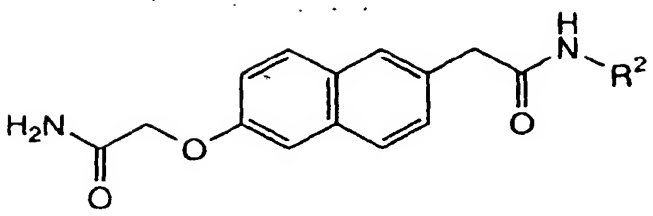

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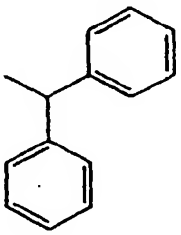
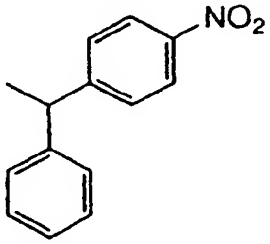
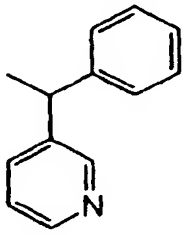
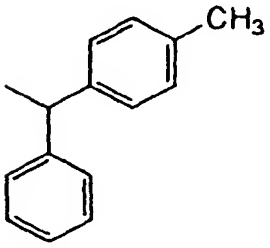
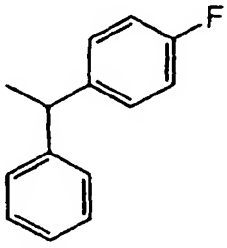
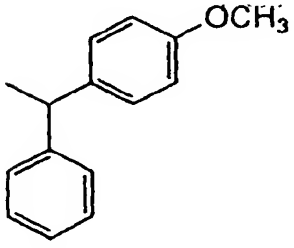
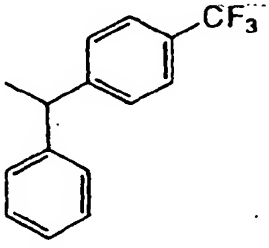

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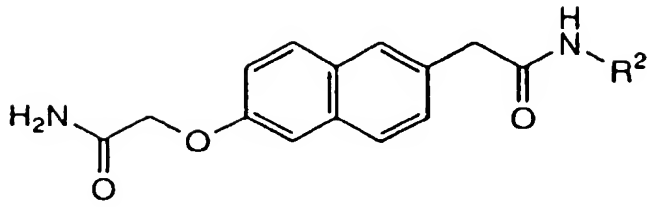

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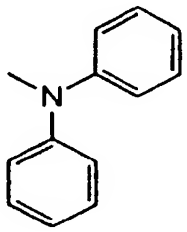
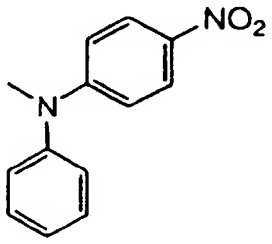
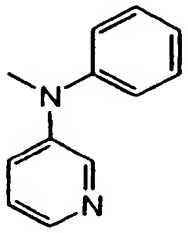
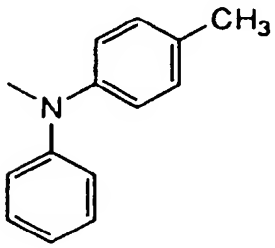
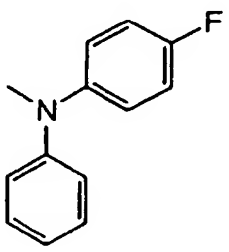
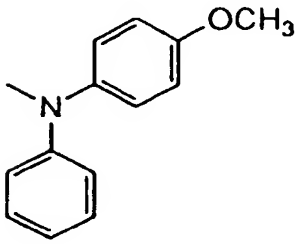
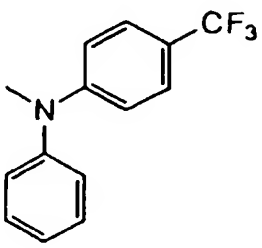

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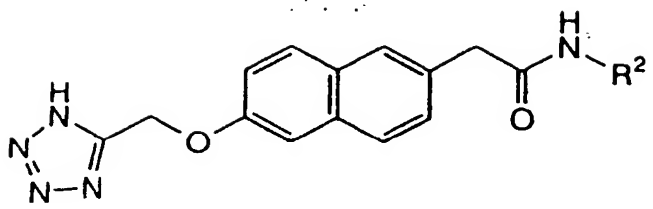

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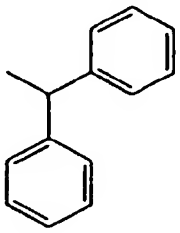
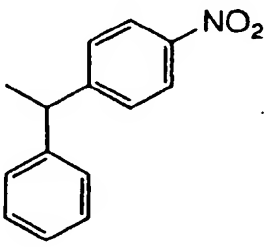
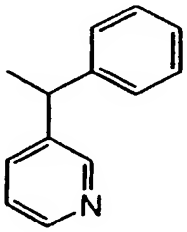
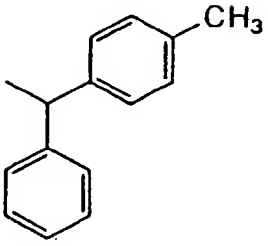
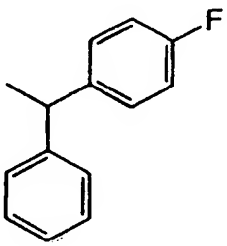
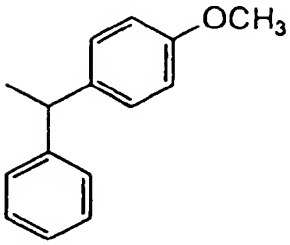
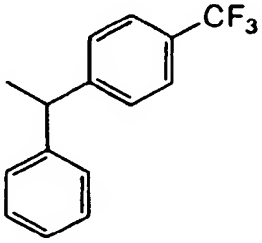

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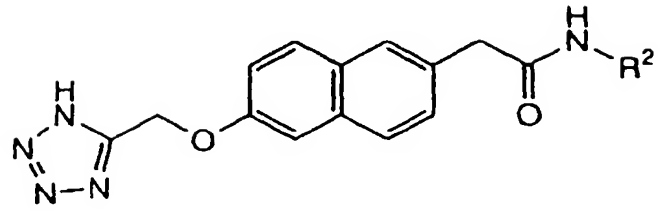

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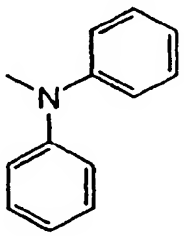
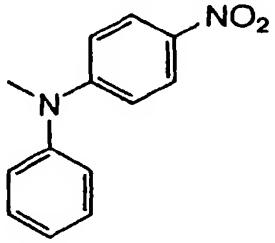
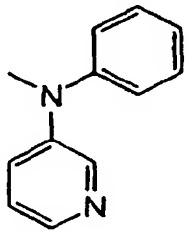
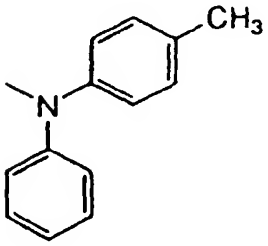
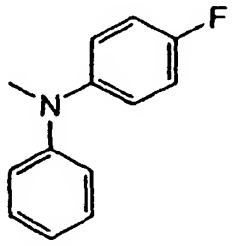
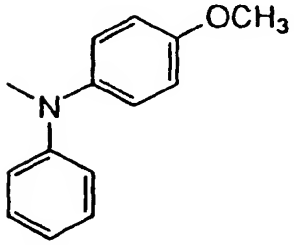
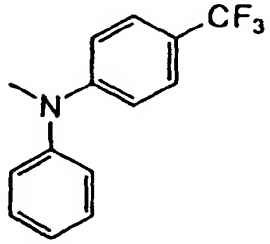

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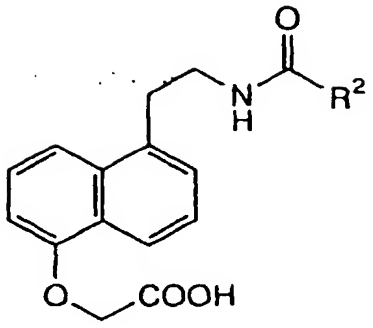

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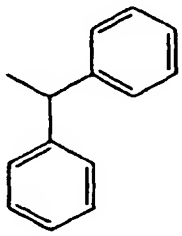
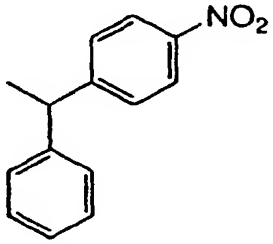
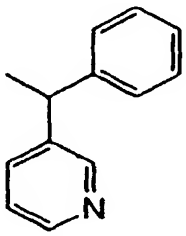
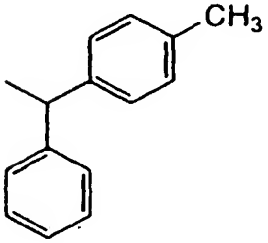
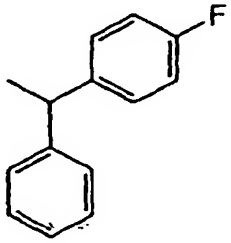
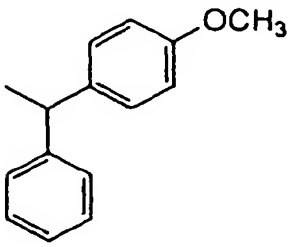
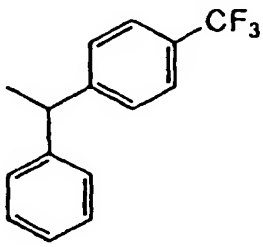

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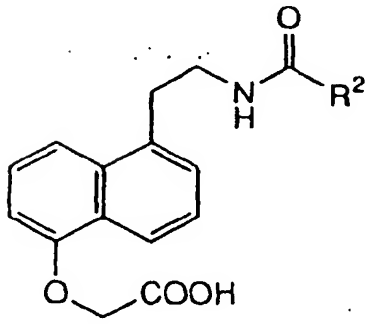

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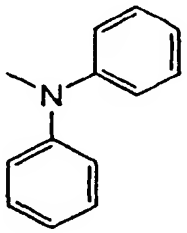
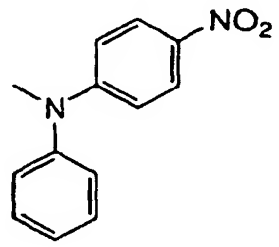
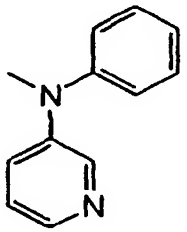
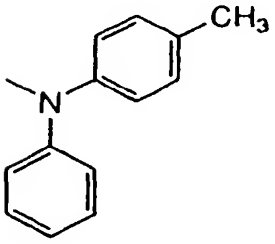
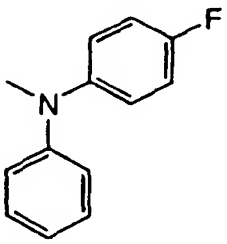
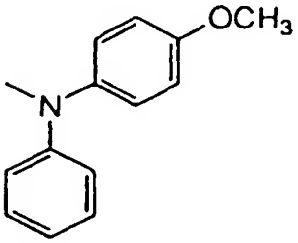
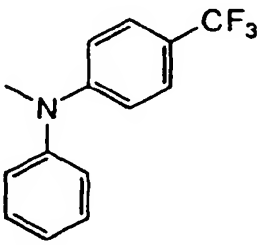

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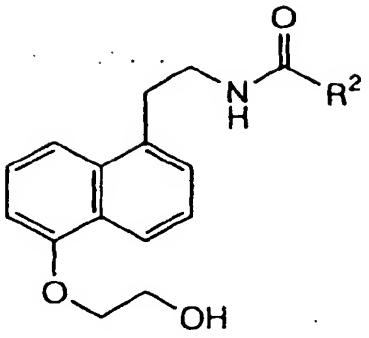

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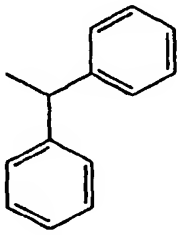
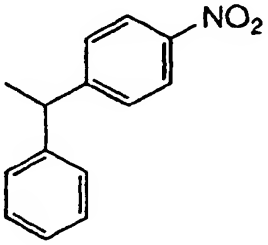
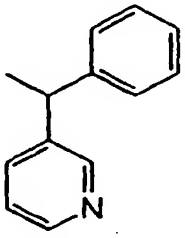
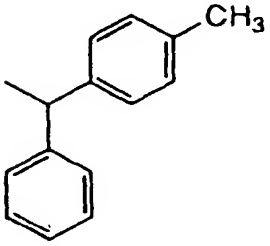
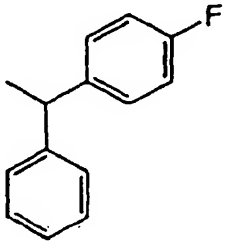
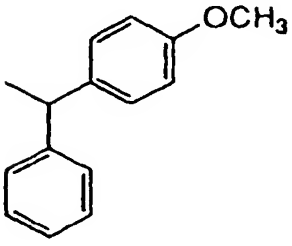
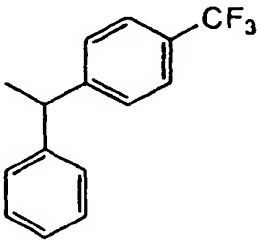

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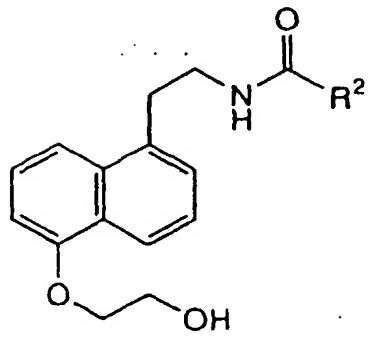

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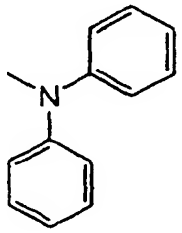
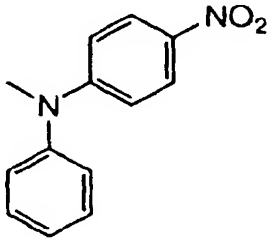
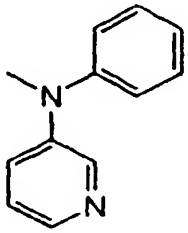
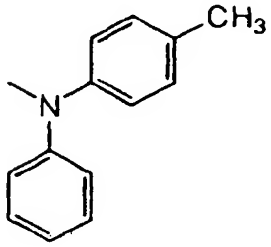
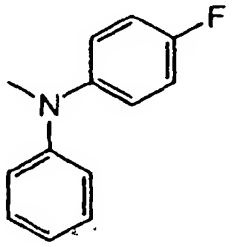
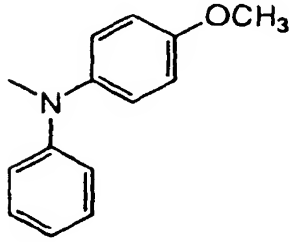
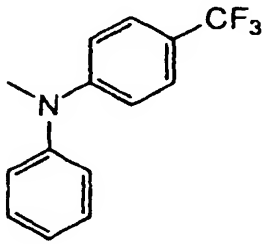

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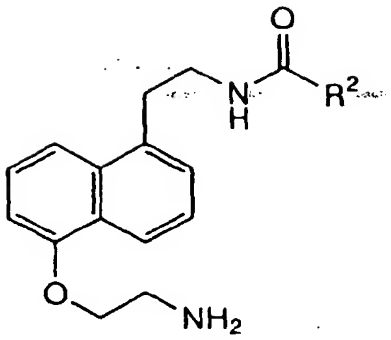

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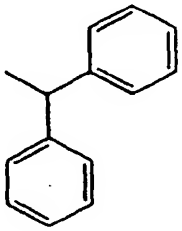
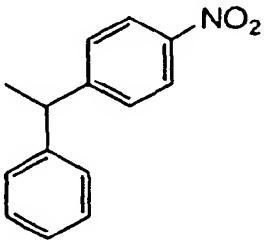
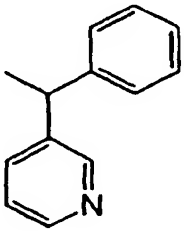
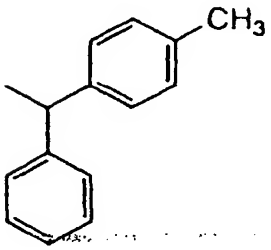
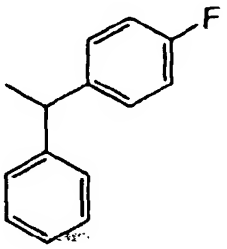
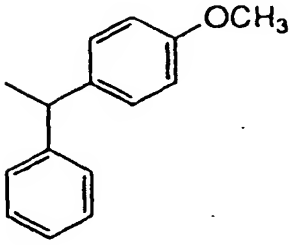
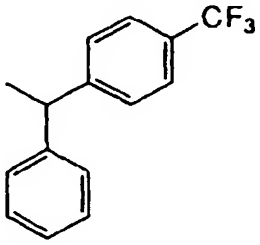

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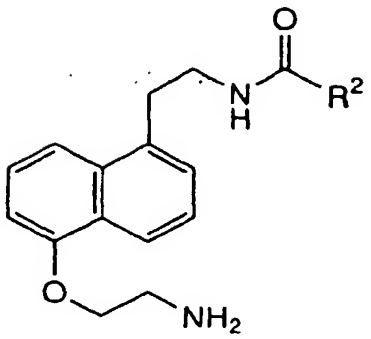

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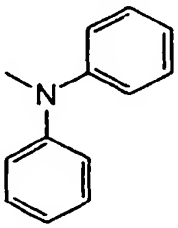
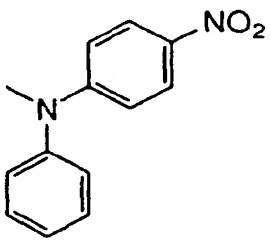
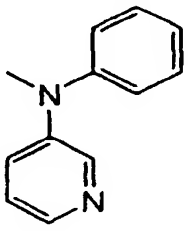
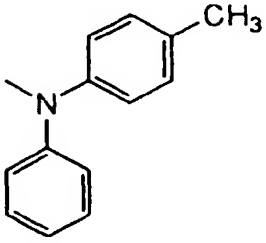
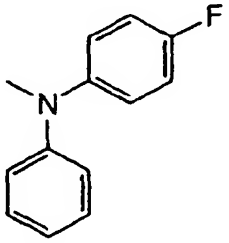
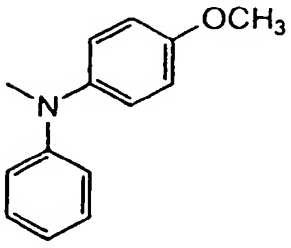
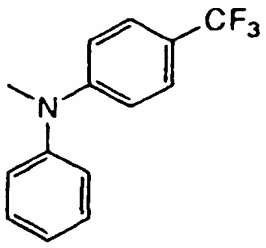

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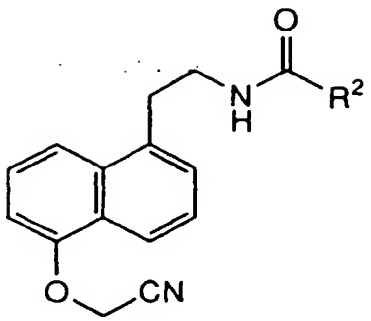

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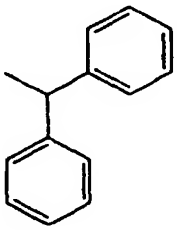
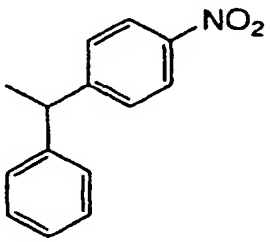
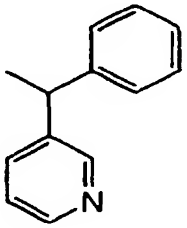
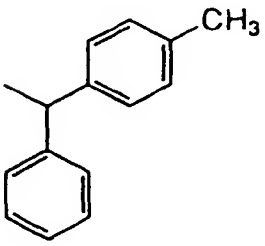
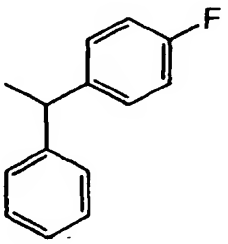
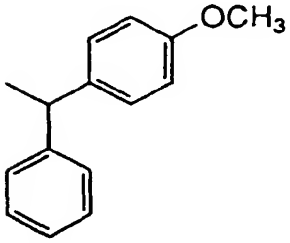
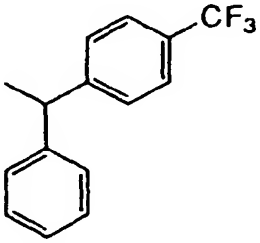

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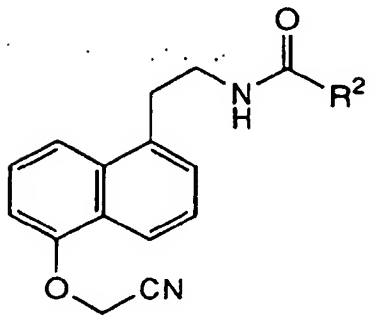

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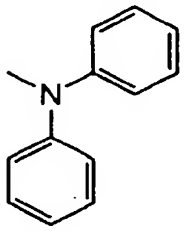
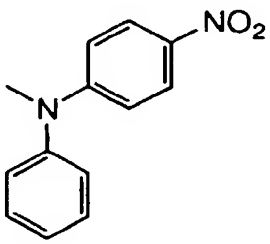
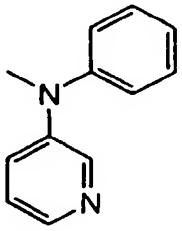
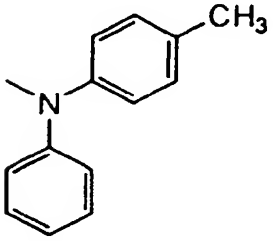
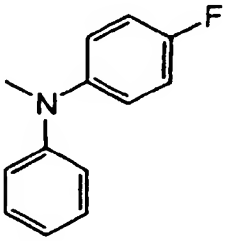
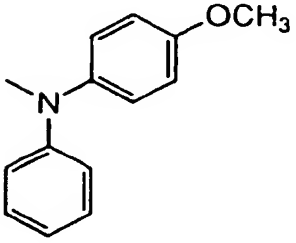
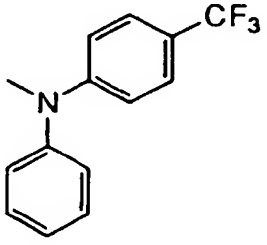

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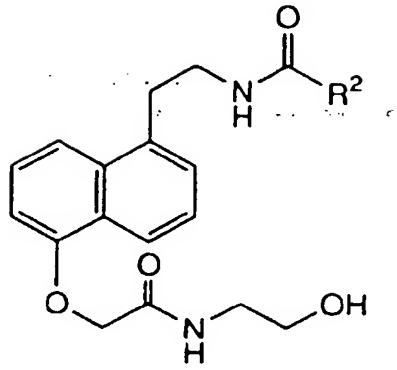

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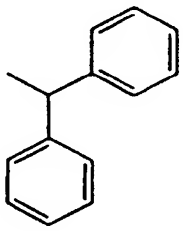
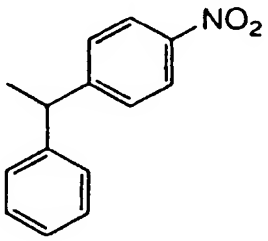
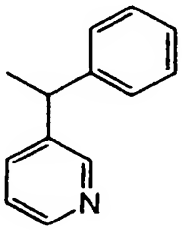
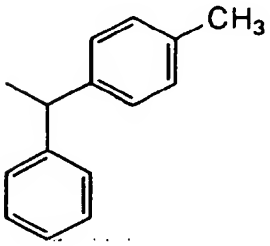
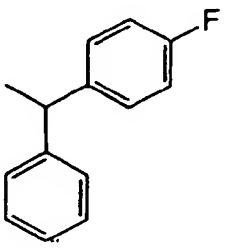
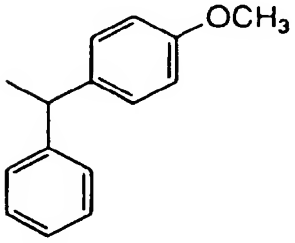
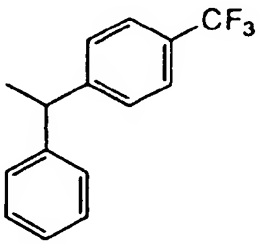

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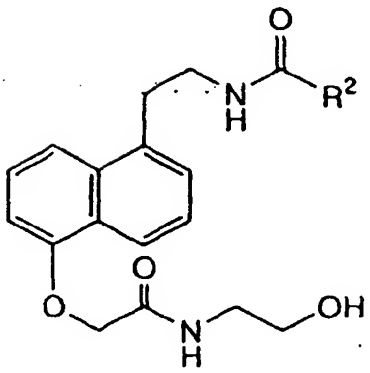

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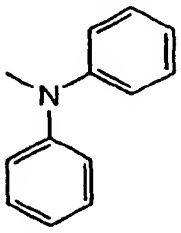
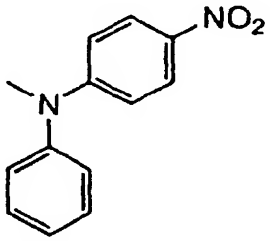
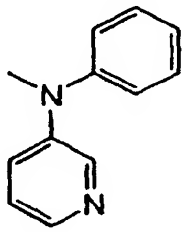
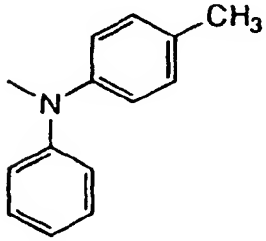
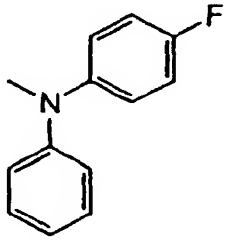
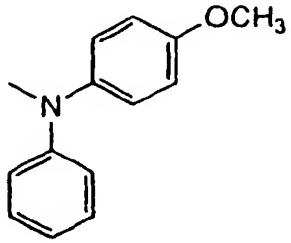
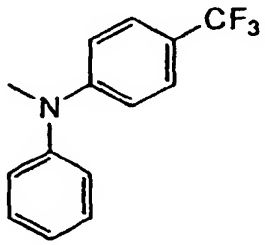

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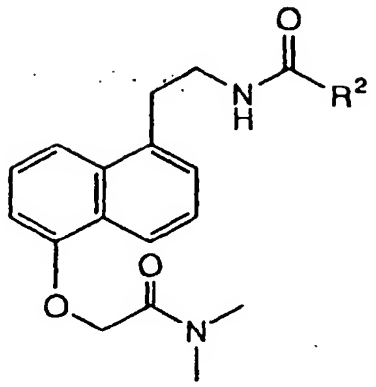

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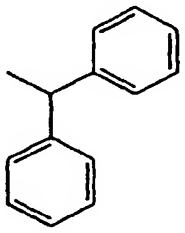
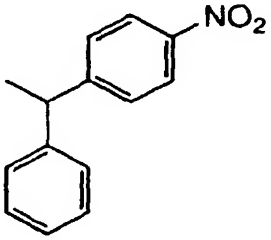
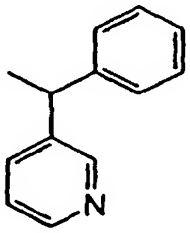
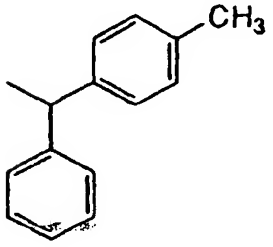
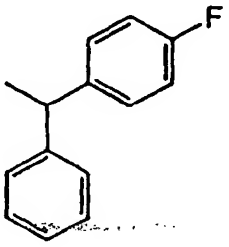
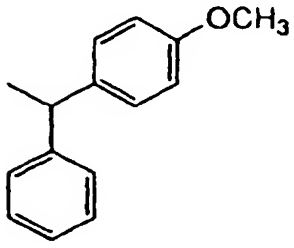
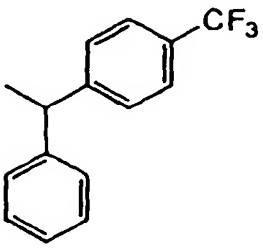

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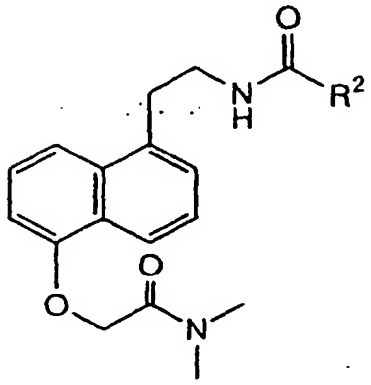

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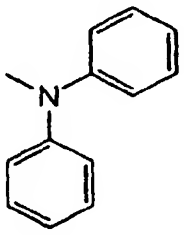 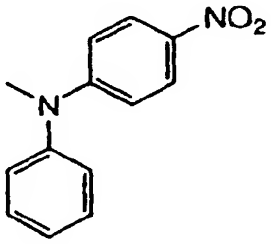 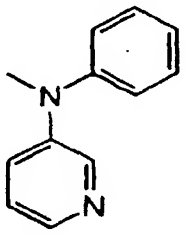
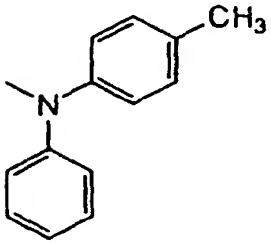 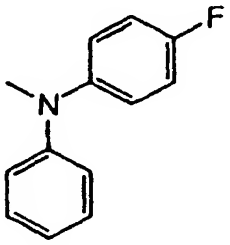
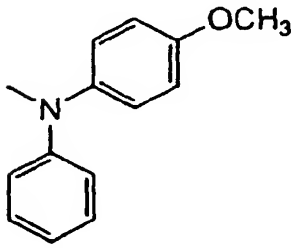 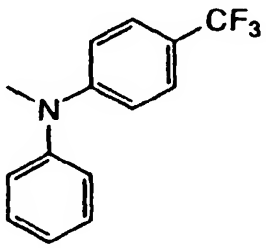

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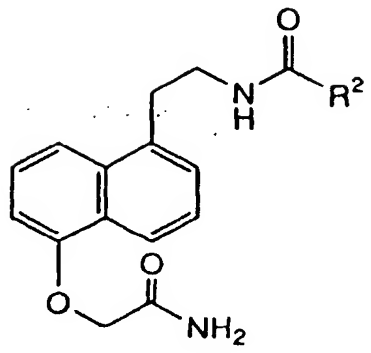

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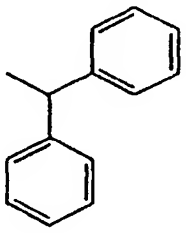
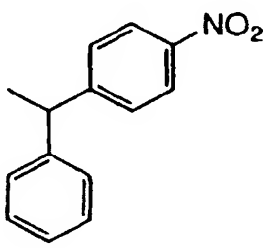
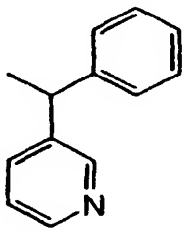
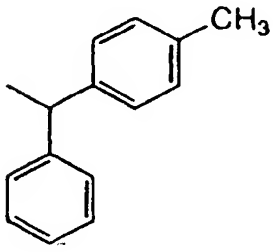
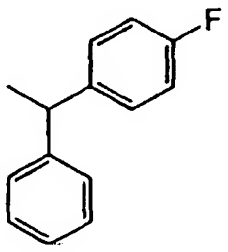
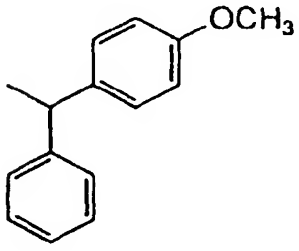
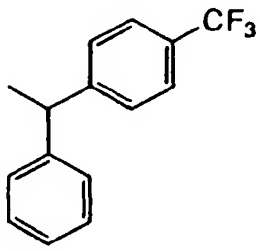

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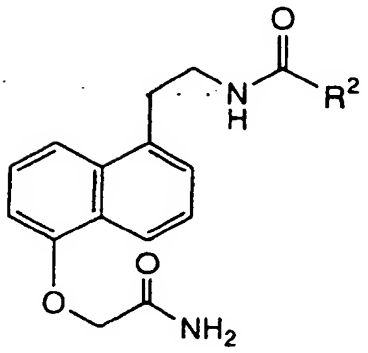

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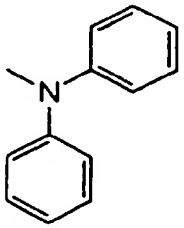
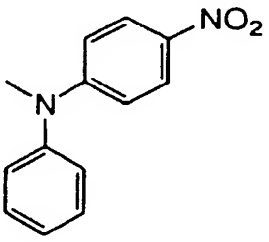
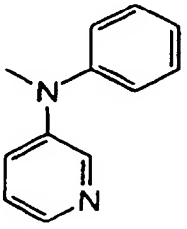
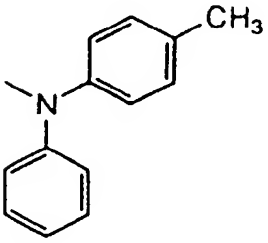
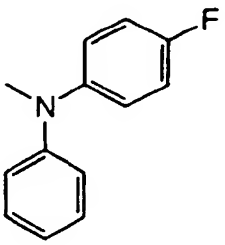
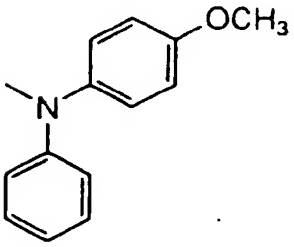
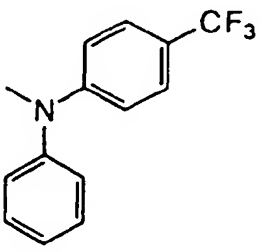

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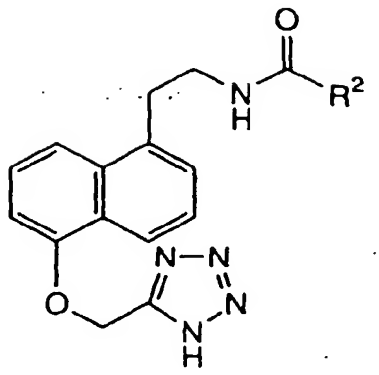

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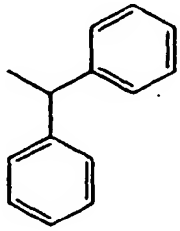
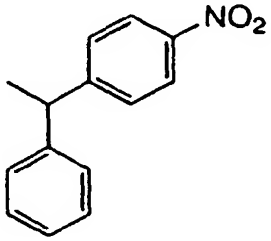
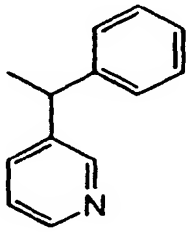
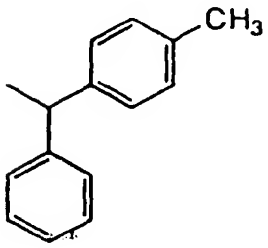
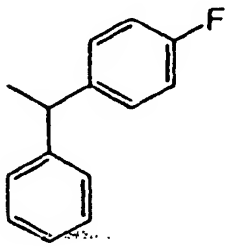
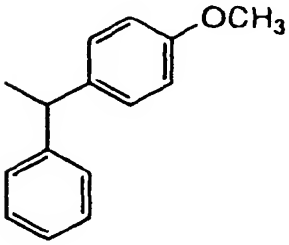
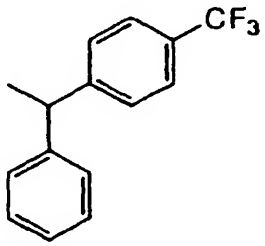

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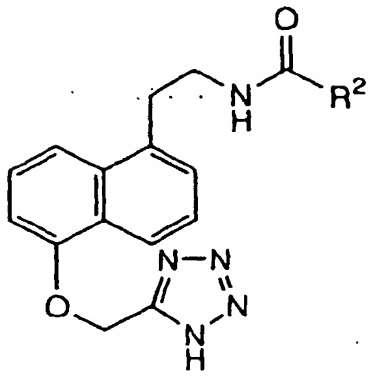

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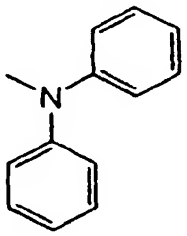
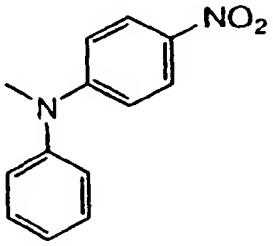
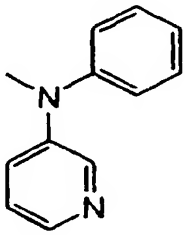
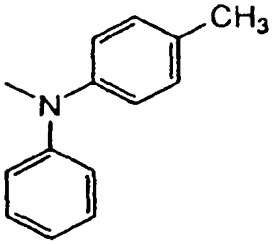
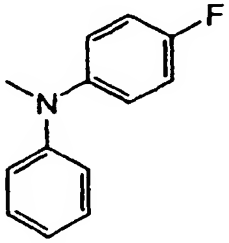
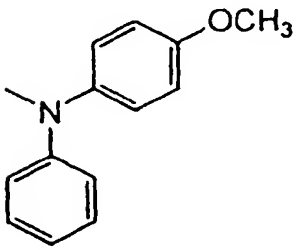
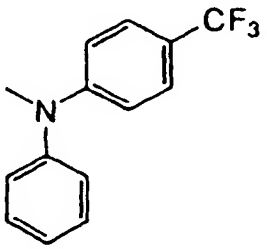

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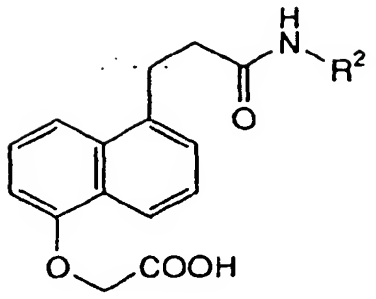

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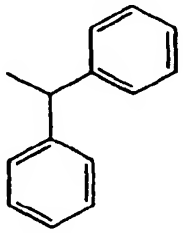
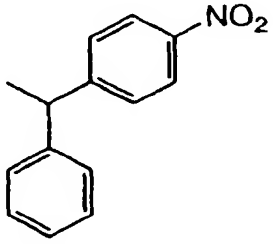
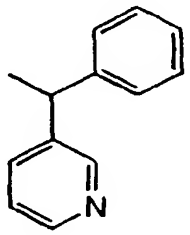
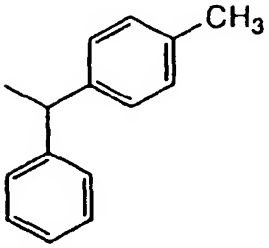
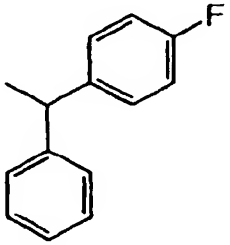
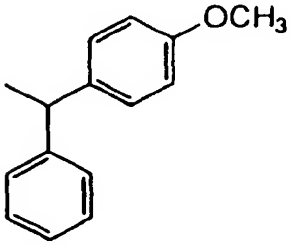
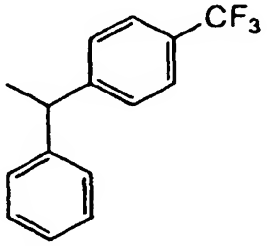

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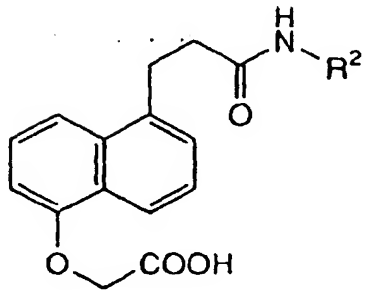

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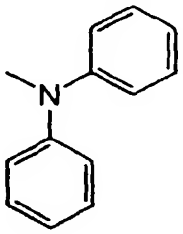
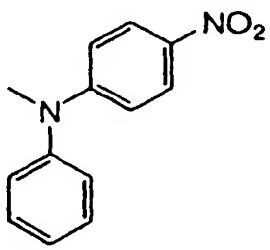
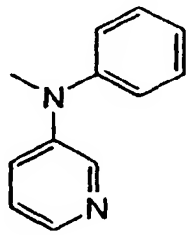
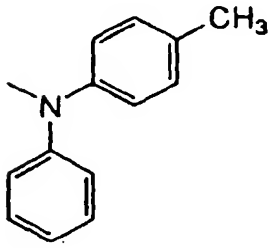
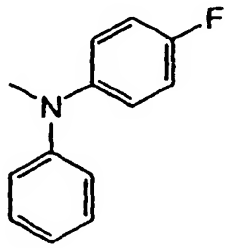
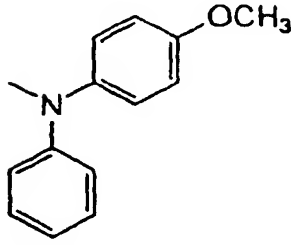
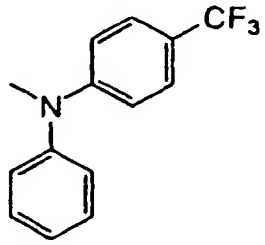

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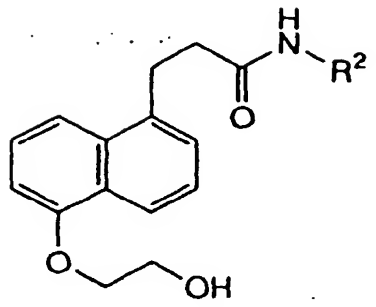

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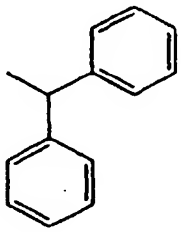
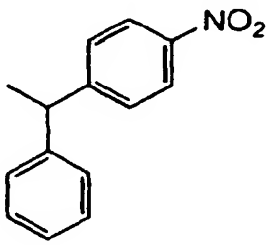
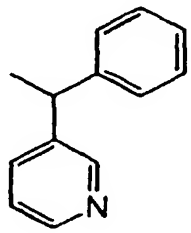
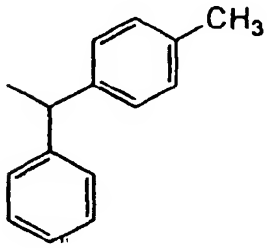
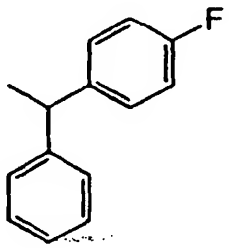
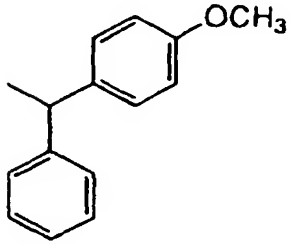
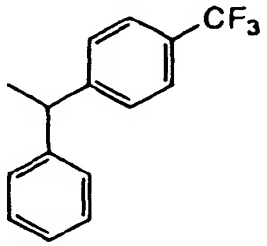

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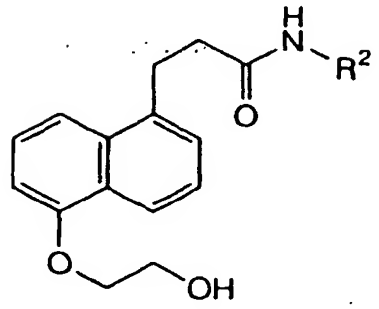

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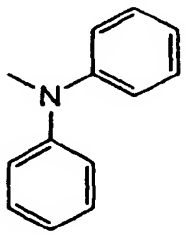
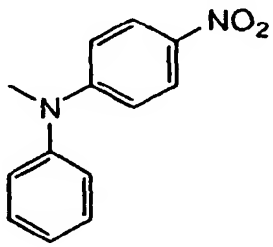
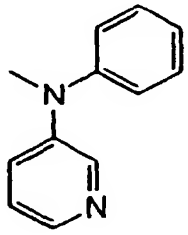
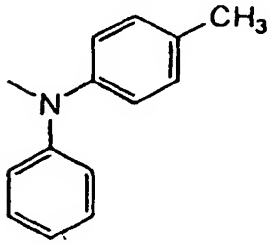
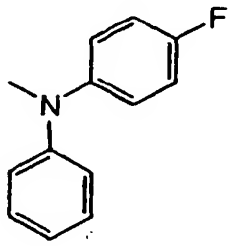
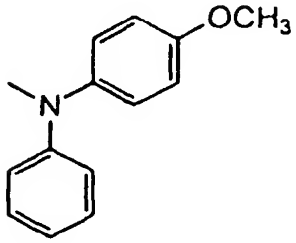
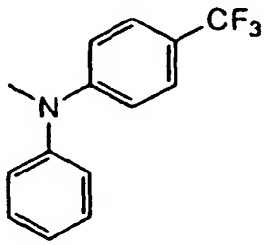

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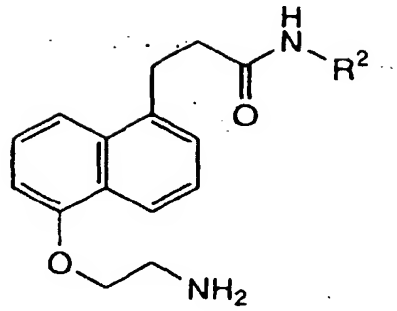
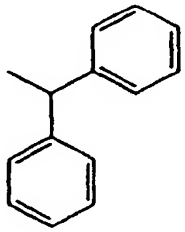
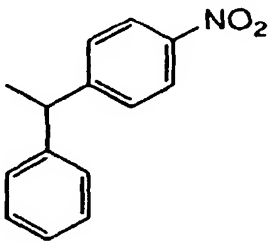
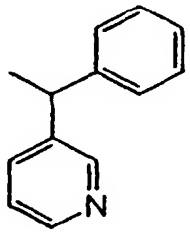
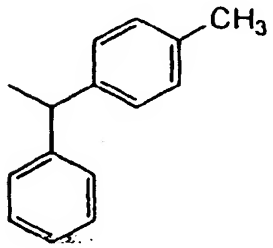
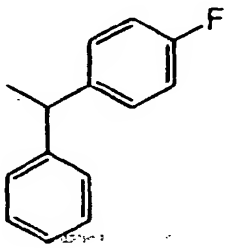
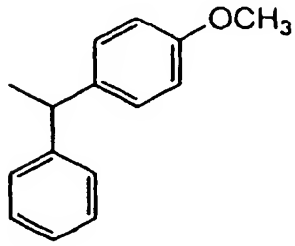
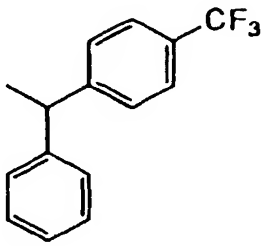


R^2








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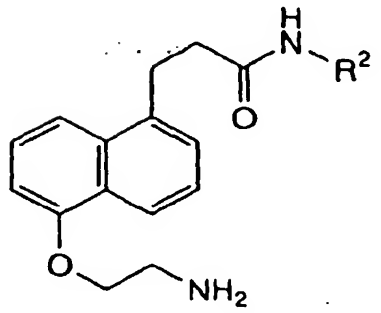
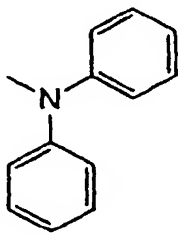
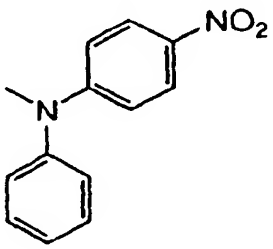
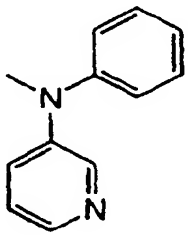
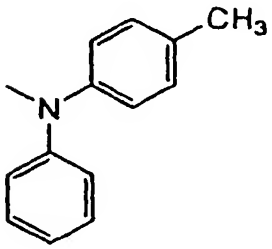
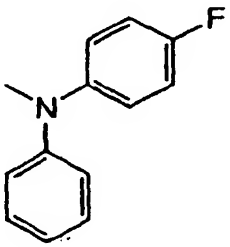
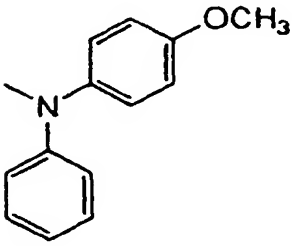
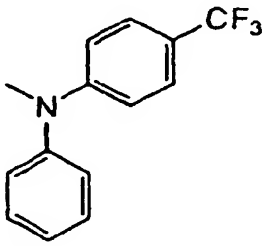


R^2








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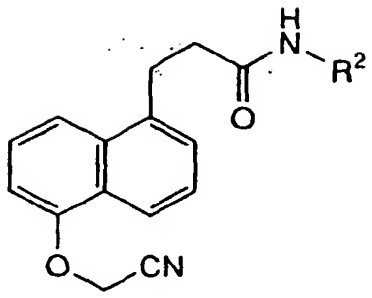

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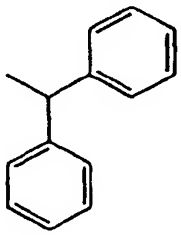
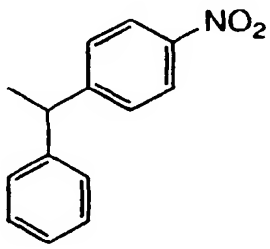
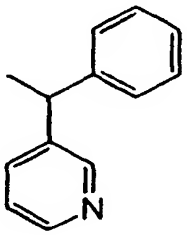
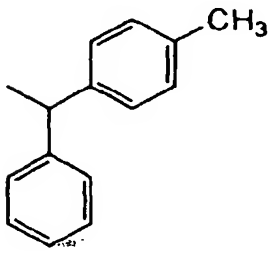
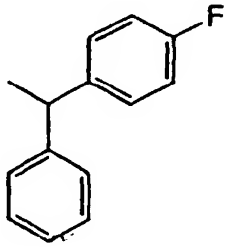
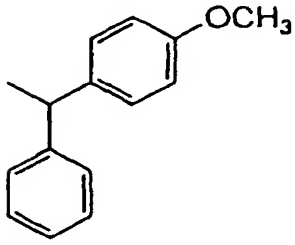
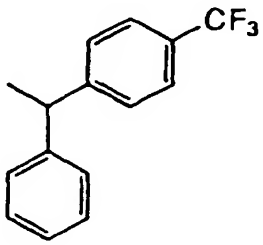

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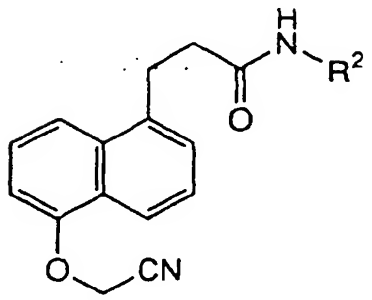

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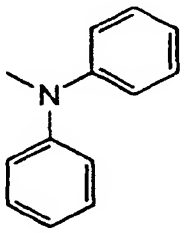
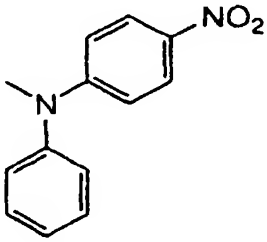
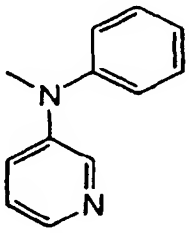
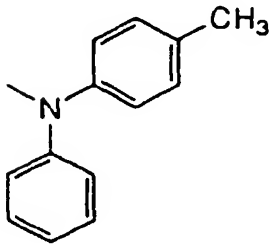
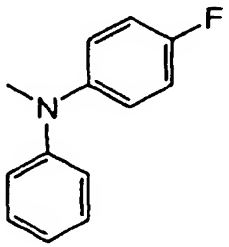
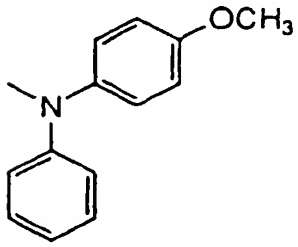
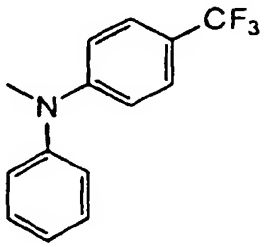

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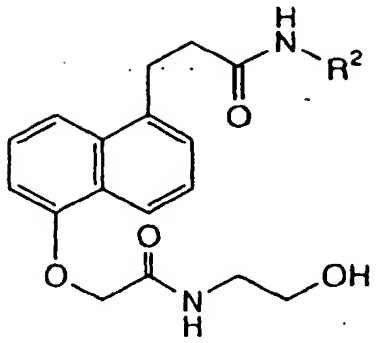

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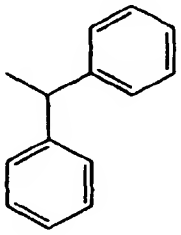
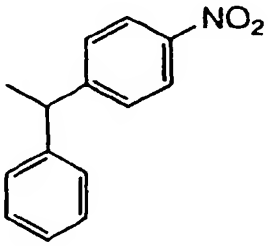
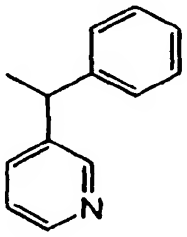
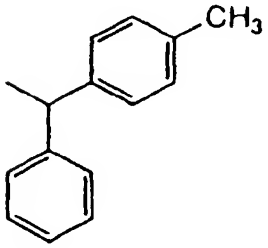
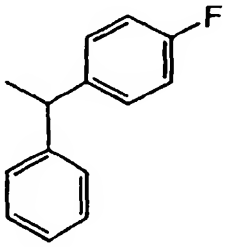
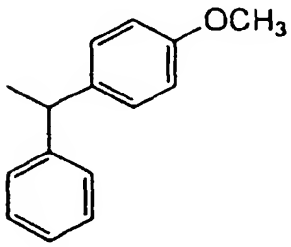
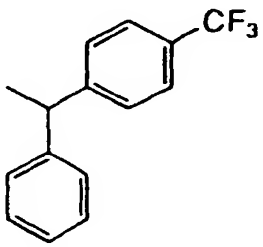

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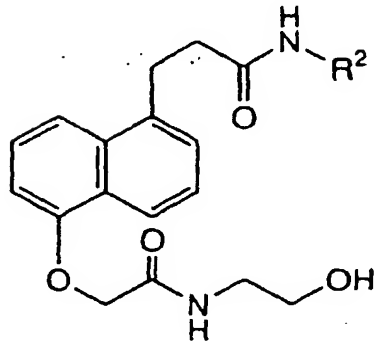

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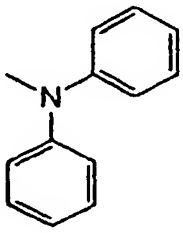
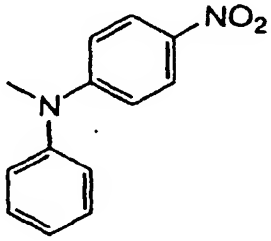
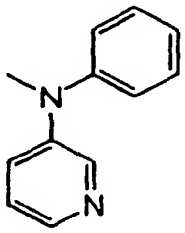
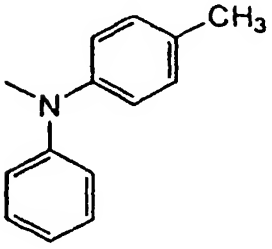
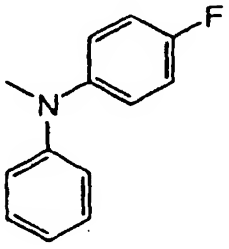
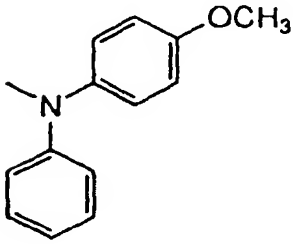
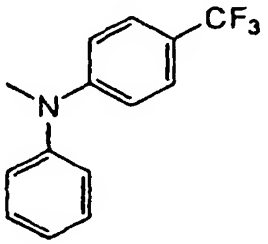

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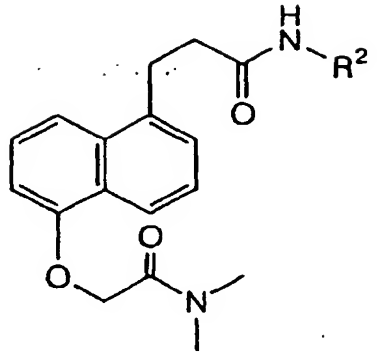

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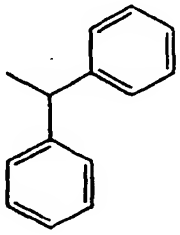
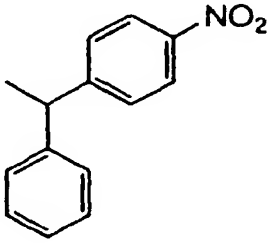
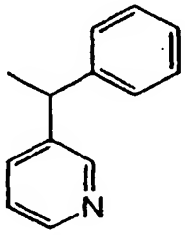
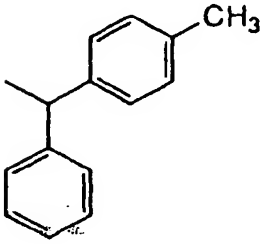
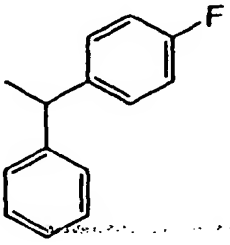
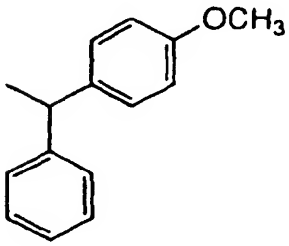
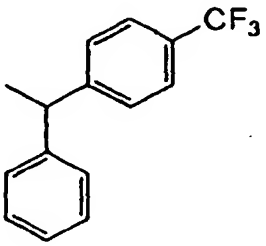

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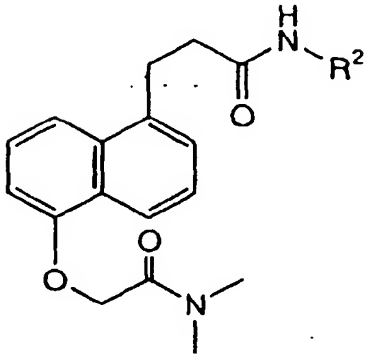

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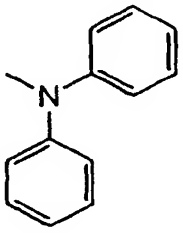
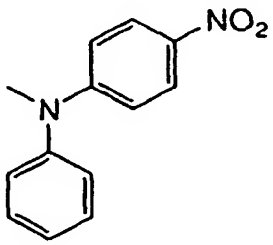
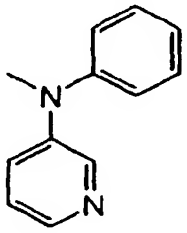
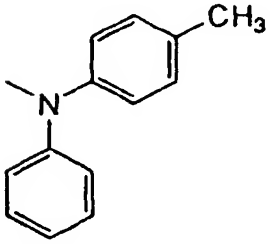
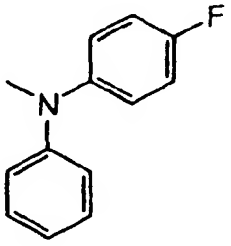
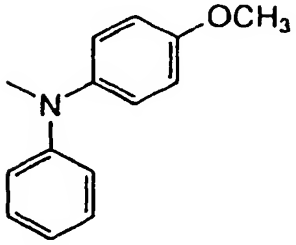
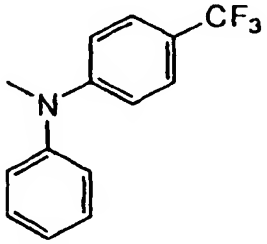

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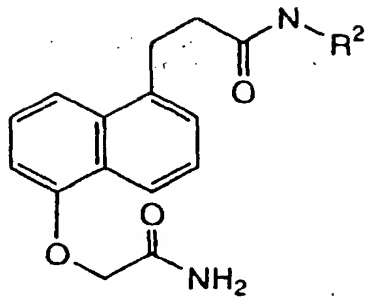

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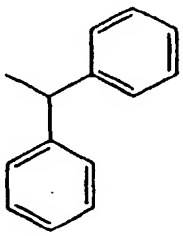
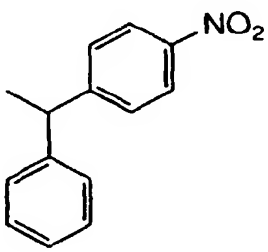
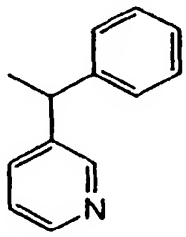
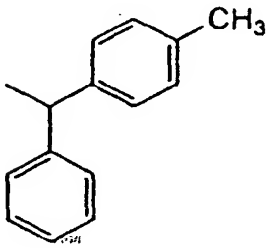
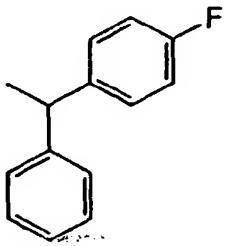
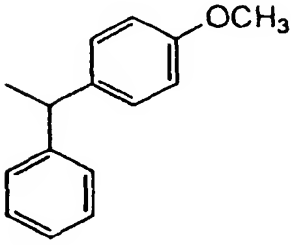
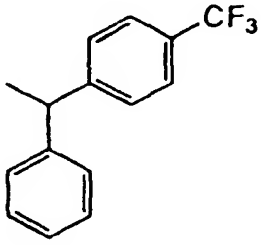

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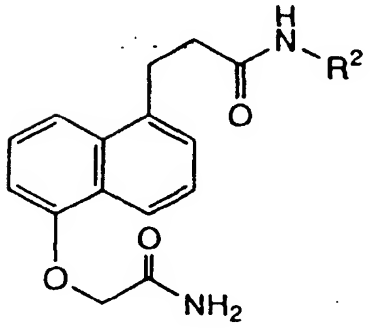


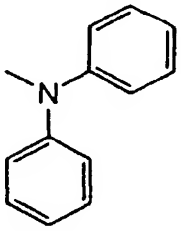
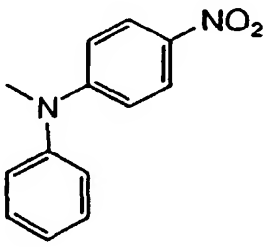
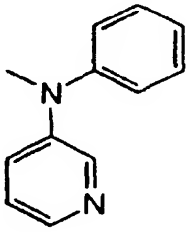
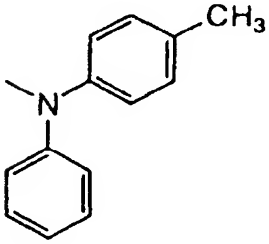
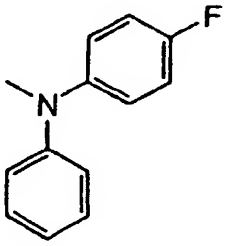
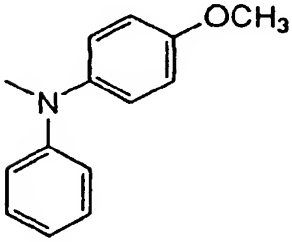
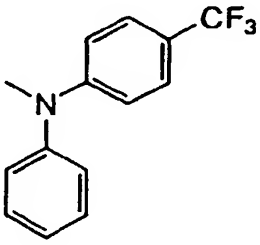
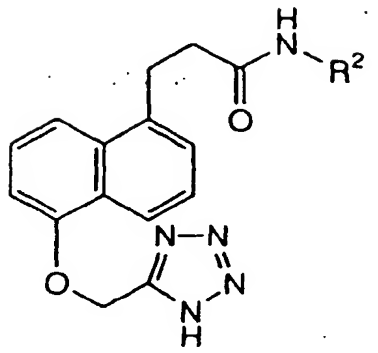
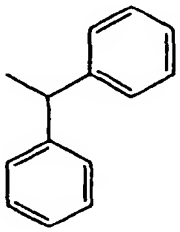
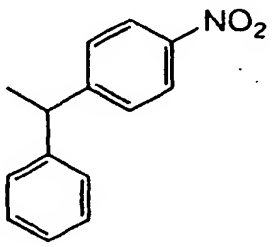
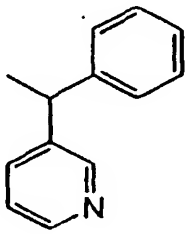
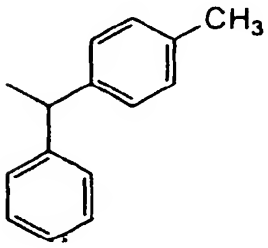
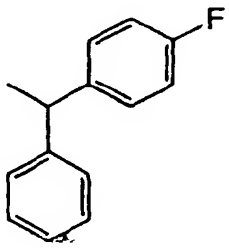
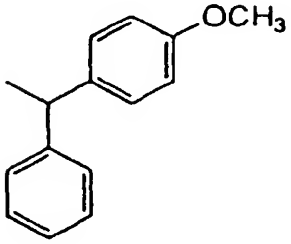
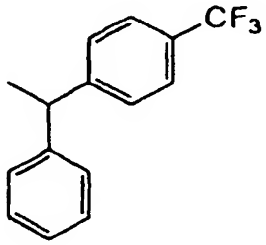
R^2








Table 48



R^2








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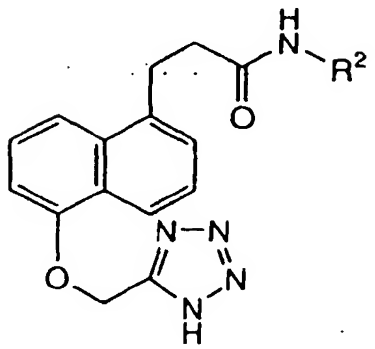


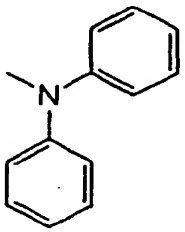
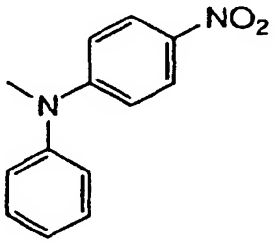
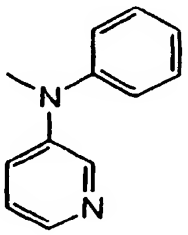
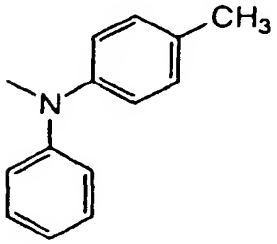
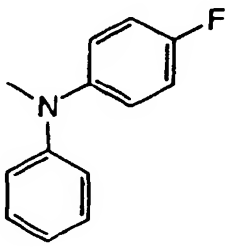
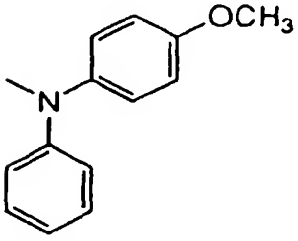
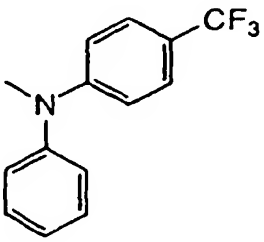
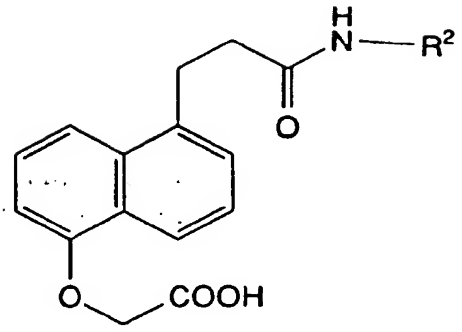
R^2








Table 49



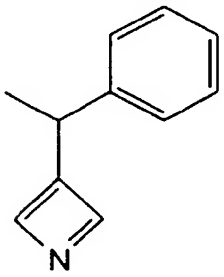
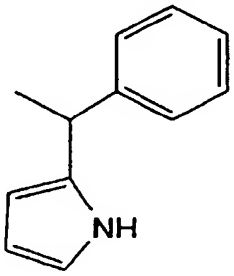
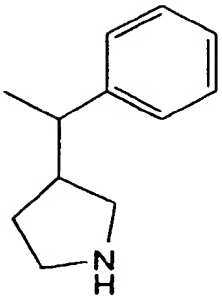
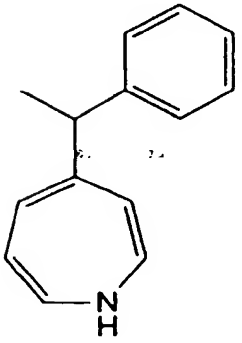
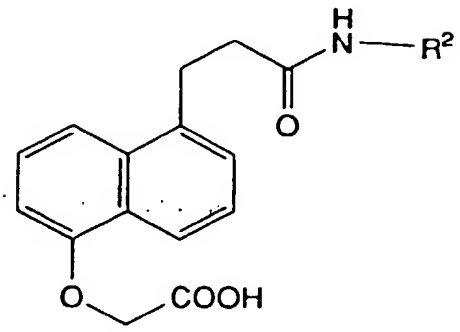
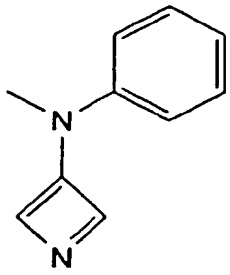
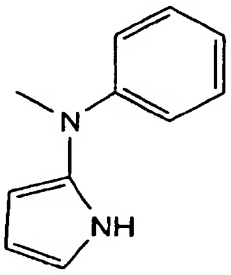
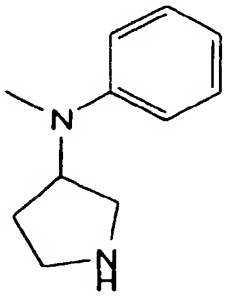
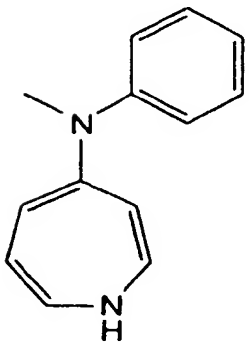
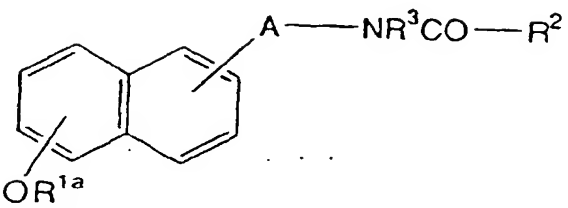
R^2





Table 49 (Continued)



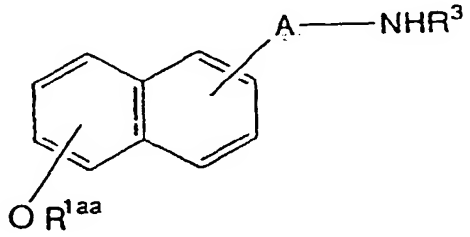
R^2





According to a feature of the present invention, compounds of the formula (I), wherein R^1 is C1-4 alkyl or (C1-4 alkylene)-$COOR^{10}$ in which R^{10} is as hereinbefore defined, and B is NR^3CO in which R^3 is as hereinbefore defined, i.e. the compounds of the formula (Ia).



(Ia)

wherein R^{1a} is C1-4 alkyl or (C1-4 alkylene)-$COOR^{10}$ in which R^{10} is as hereinbefore defined and the other symbols are as hereinbefore defined may be prepared by reacting the compounds of the formula (II)



(II)

wherein R^{1aa} is C1-4 alkyl or (C1-4 alkylene)-$COOR^{10a}$ in which R^{10a} is C1-4 alkyl, and the other symbols are as hereinbefore defined with the compounds of the formula (III)

$$HOOC\text{-}R^2 \qquad \text{(III)}$$

wherein R^2 is as hereinbefore defined to form an amide-bond, optionally followed by hydrolysis under alkaline conditions.

The reaction to form an amide bond is well known. It may be carried out, for example:

(1) using an acid halide
(2) using a mixed acid anhydride
(3) using a condensing agent (e.g. 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC) or dicyclohexylcarbodiimide (DCC)).

Concrete description of the methods described above are as follows:

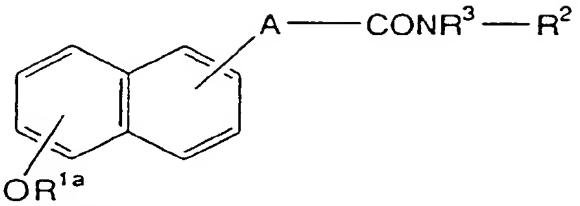
(1) method using an acid halide may be carried out, for example; carboxylic acid is reacted with an acid halide (e.g. oxalyl chloride or thionyl chloride) in an inert organic solvent (e.g. chloroform, methylene chloride, diethylether or tetrahydrofuran (THF)) or without solvents at from -20°C to the reflux temperature of the solvent used to give an acid halide. The obtained acid halide and an amine are reacted in an inert organic solvent (e.g. chloroform, methylene chloride, diethylether or THF) in the presence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine) at 0-40°C.
(2) method using a mixed acid anhydride may be carried out, for example; carboxylic acid is reacted with an acid halide (e.g. pivaloyl chloride, tosyl chloride or mesyl chloride) or an acid derivative (e.g. ethyl chloroformate or isobutyl chloroformate) in an inert organic solvent (e.g. chloroform, methylene chloride, diethyl ether or THF) or without solvents, in the presence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine), at 0-40°C.
(3) method using a condensing agent such as EDC or DCC may be carried out, for example; a carboxylic acid and an amine are reacted in an inert organic solvent (e.g. chloroform, methylene chloride, diethylether or THF) or without solvents in the presence or absence of a tertiary amine (e.g. pyridine, triethylamine, dimethylaniline or dimethylaminopyridine) using a condensing agent such as EDC or DCC at 0-40°C.

Preferably, the reactions (1), (2) and (3) described above are carried out under an atmosphere of inert gas (e.g. argon or nitrogen) under anhydrous conditions.

The hydrolysis under alkaline conditions is known. For example, hydrolysis may be carried out in a water-miscible organic solvent (e.g. methanol, ethanol, dimethoxyethane or a mixture thereof), using an alkali (e.g. sodium hydroxide or potassium hydroxide), at 0-50°C.

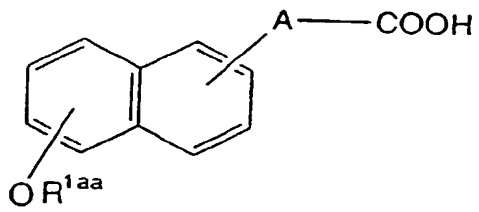
According to a further feature of the present invention, compounds of the formula (I), wherein R^1 is C1-4 alkyl or (C1-4 alkylene)-$COOR^{10}$ in which R^{10} is as hereinbefore defined, and B is $CONR^3$ in which R^3 is as hereinbefore

defined, i.e. the compounds of the formula (Ib)



(Ib)

wherein all symbols are as hereinbefore defined may be prepared by reacting the compounds of the formula (IV)



(IV)

wherein all symbols are as hereinbefore defined with the compounds of the formula (V)

$$R^3HN\text{-}R^2 \qquad (V)$$

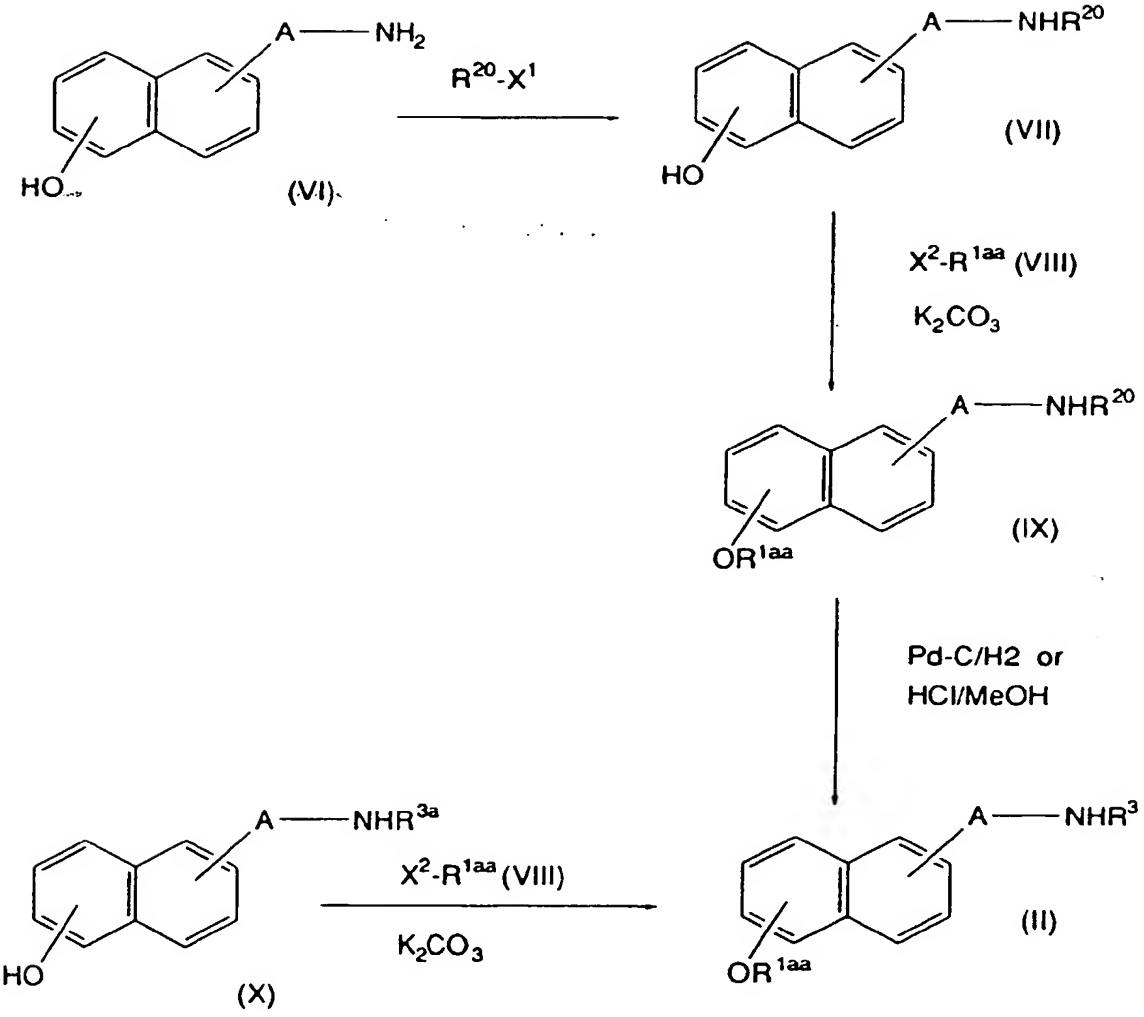
wherein all symbols are as hereinbefore defined to form an amide-bond, optionally followed by hydrolysis under alkaline conditions.

Forming an amide-bond or hydrolysis under alkaline conditions may be carried out by the methods as hereinbefore described.

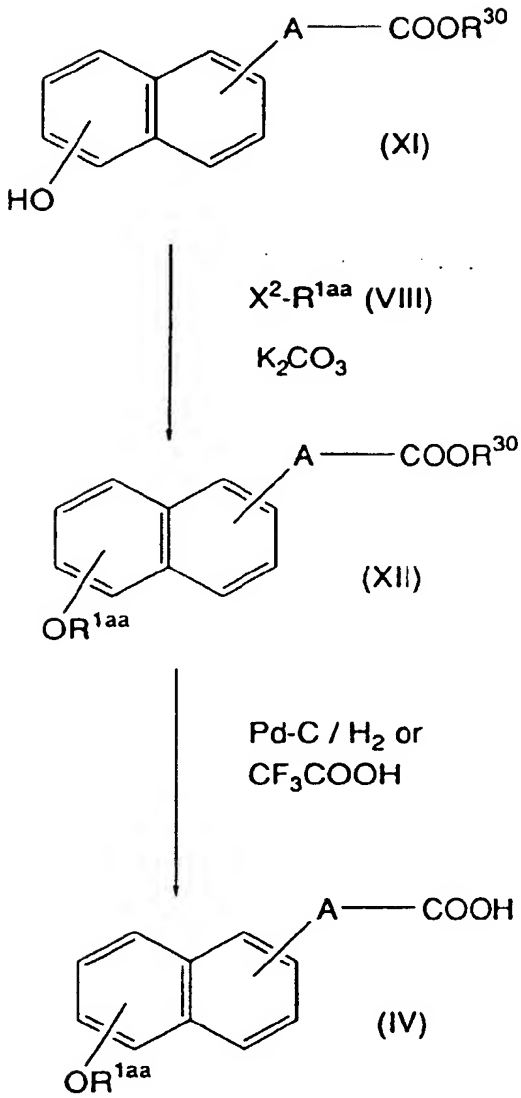
The compounds of the formula (II) and (IV) may be prepared according to the reaction of the following Schemes (A) and (B), respectively.

In the Schemes (A) and (B), R^{3a} is C1-4 alkyl, R^{20} is t-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz), R^{30} is benzyl or t-butyl, X^1 and X^2 each, independently, is halogen, and the other symbols are as hereinbefore defined.

Scheme (A)



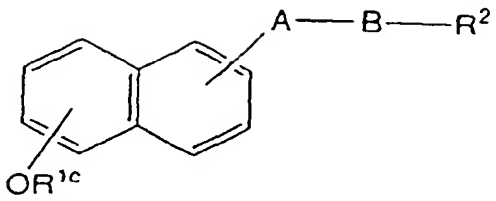
Scheme (B)



According to a further feature of the present invention, compounds of the formula (I), wherein R^1 is

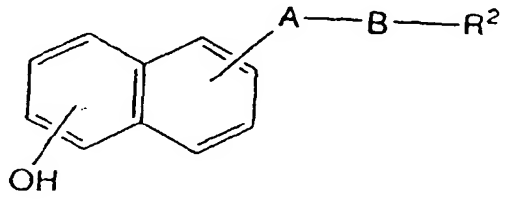
(C1-4 alkylene)-$COOR^{10}$,
(C1-4 alkylene)-OH,
(C1-4 alkylene)-$CONR^4R^5$,
(C1-4 alkylene)-$CONR^6$-(C1-4 alkylene)-OH,
(C1-4 alkylene)-NR^4R^5,
(C1-4 alkylene)-cyano or
(C1-4 alkylene)-tetrazolyl

in which all symbols are as hereinbefore defined, i.e. the compounds of the formula (Ic)



(Ic)

wherein R^{1c} is (C1-4 alkylene)-$COOR^{10}$, (C1-4 alkylene)-OH, (C1-4 alkylene)-$CONR^4R^5$, (C1-4 alkylene)-$CONR^6$-(C1-4 alkylene)-OH, (C1-4 alkylene)-NR^4R^5, (C1-4 alkylene)-cyano or (C1-4 alkylene)-tetrazolyl and the other symbols are as hereinbefore defined may be prepared by reacting the compounds of the formula (Id)



(Id)

wherein all symbols are as hereinbefore defined with the compounds of the formula

$$X^3\text{-}R^{1ca}$$

wherein X^3 is halogen and R^{1ca} is

(C1-4 alkylene)-$COOR^{10a}$,
(C1-4 alkylene)-OR^{30a},
(C1-4 alkylene)-$CONR^4R^{5a}$,
(C1-4 alkylene)-$CONR^6$-(C1-4 alkylene)-OR^{30a},
(C1-4 alkylene)-NR^4R^{5a},
(C1-4 alkylene)-cyano,
(C1-4 alkylene)-tetrazolyl-R^{30a}

in which, R^{5a} is C1-4 alkyl, cbz or boc, R^{30a} is tetrahydropyranyl, cbz or boc, optionally followed by hydrolysis under alkaline conditions or by removal of the protecting group.

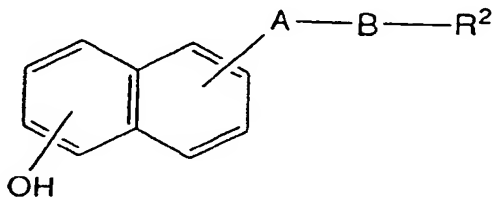
O-alkylation is known, and for example, this reaction may be carried out in a water-miscible organic solvent (e.g. acetone, THF or methylene chloride) in the presence of a base (e.g. potassium carbonate), at 0-50°C.

The hydrolysis under alkaline conditions may be carried out by the method as hereinbefore described.

Removal of the protecting group may be carried out by known methods. For example, removal of cbz may be carried out under an atmosphere of hydrogen gas, in an organic solvent (e.g. methanol, ethanol or THF), using a catalyst (e.g. Pd-C, Pd or Ni), at 0-50°C. Removal of tetrahydropyranyl and boc may be carried out in a water-miscible organic solvent (e.g. methanol, ethanol, THF or dioxane), using an organic acid (e.g. acetic acid, p-toluenesulfonic acid, trifluoroacetic acid or trichloroacetic acid) or an inorganic acid (e.g. hydrochloric acid or hydrobromic acid), at 0-90°C.

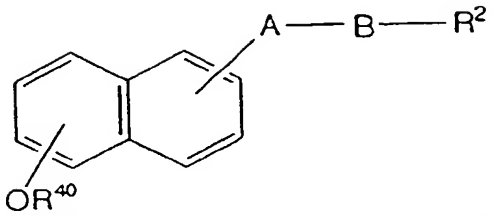
According to a further feature of the present invention, compounds of the formula (Ic) wherein R^{1c} is (C1-4 alkylene)-tetrazolyl may be prepared by reacting compounds of the formula (Ic) wherein R^{1c} is (C1-4 alkylene)-cyano with sodium azide in an organic solvent (e.g. dihydrofuran (DHF)), in the presence of ammonium chloride.

According to a further feature of the present invention, compounds of the formula (I), wherein R^1 is hydrogen, i.e. the compounds of the formula (Id)



(Id)

wherein all symbols are as hereinbefore defined may be prepared from the compounds of the formula (XIII)



(XIII)

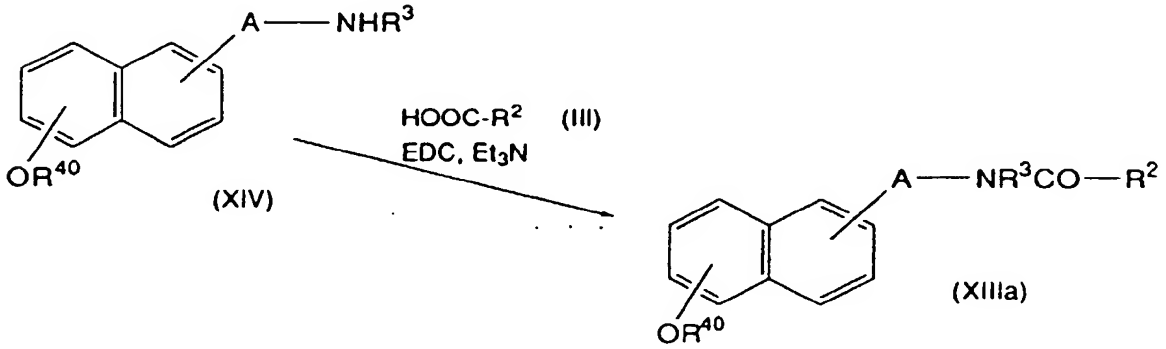
wherein R^{40} is C1-4 alkyl or benzyl and the other symbols are as hereinbefore defined, by reduction or by removal of alkyl.

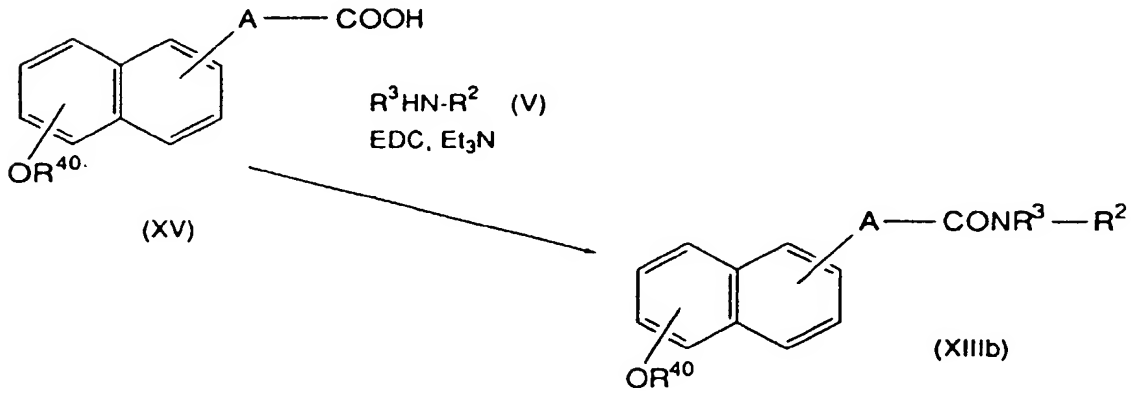
The reduction reaction is known, and for example, this reaction may be carried out under an atmosphere of hydrogen gas, in an organic solvent (e.g. methanol, ethanol or THF), in the presence of a reduction catalyst (e.g. Pd-C, Pd or Ni) at 0-50°C.

The reaction for the removal of alkyl is known, and for example, this reaction may be carried out in an inert organic solvent (e.g. methylene chloride or chloroform) using BBr_3, at 0-50°C.

The compounds of the formula (XIII) may be prepared according to the reactions of the following Scheme (C).

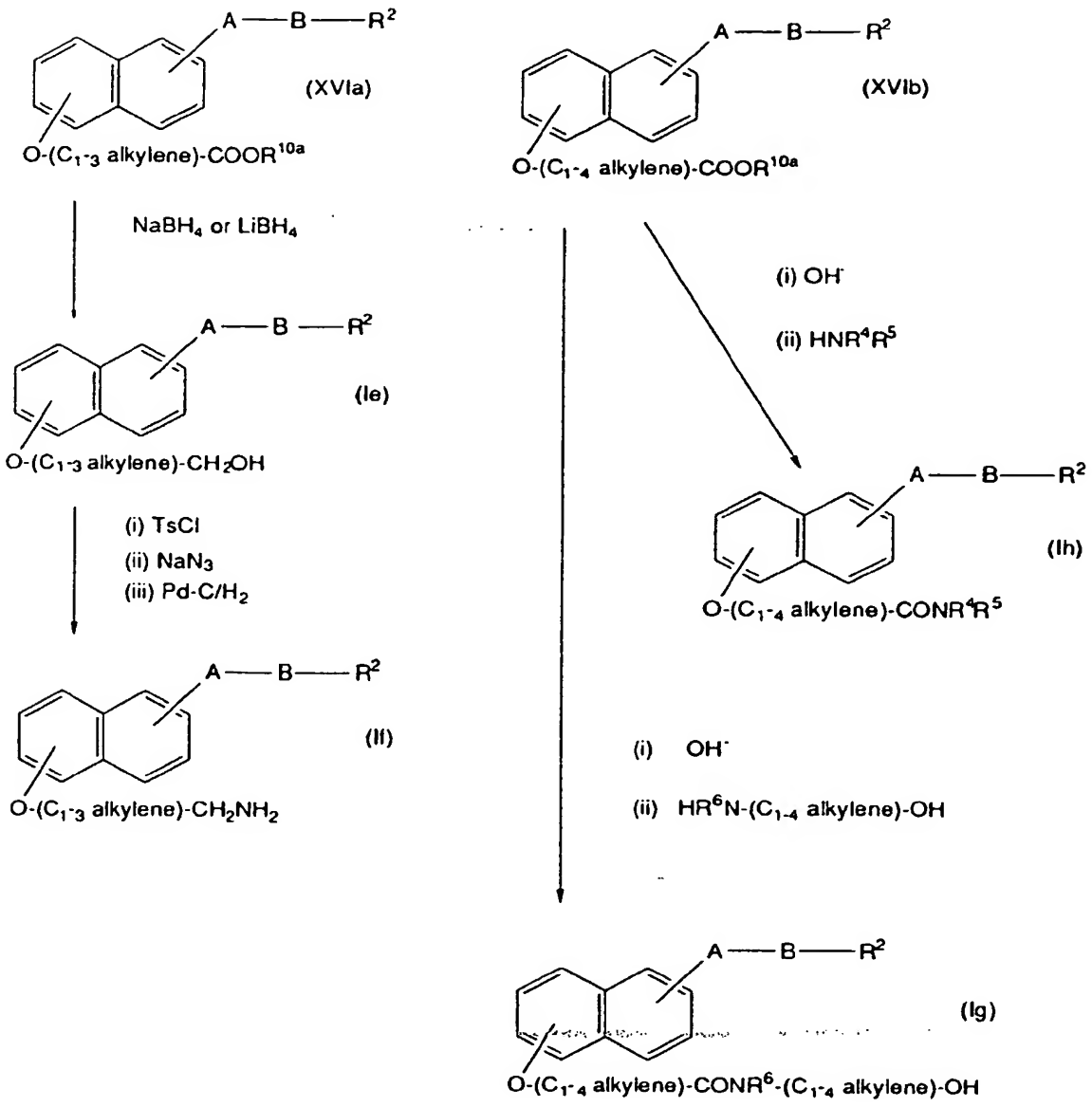
Scheme (C)





According to a further feature of the present invention, compounds of formula (I) wherein R^1 is (C1-3 alkylene)-CH_2OH, (C1-3 alkylene)-CH_2NH_2, (C1-4 alkylene)-$CONR^4R^5$ and (C1-4 alkylene)-$CONR^6$-(C1-4 alkylene)-OH, i.e. compounds of the formulae (Ie) to (Ih) respectively, may be prepared according to the reactions of the following Scheme (D).

Scheme (D)



In each reaction in the present specification, obtained products may be purified by conventional techniques. For example, purification may be carried out by distillation at atmospheric or reduced pressure, by high performance liquid chromatography, by thin layer chromatography or by column chromatography using silica gel or magnesium silicate, by washing or by recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

The starting materials and reagents in the present invention are known *per se* or may be prepared by known methods.

The compounds of the present invention of the formula (I) are useful as PGE_2 antagonists or agonists, because they bind onto prostaglandin E_2 receptors and have antagonist or agonist activity on their action.

For example, in standard laboratory tests, the activities of the compounds of the present invention were confirmed by their inhibitory effect on the binding of PGE_2 using expression cell of mouse receptor.

Binding assay using expression cell of prostanoide receptor subtype

The preparation of membrane fraction was carried out according to the method of Sugimoto *et al* [J. Biol. Chem. 267, 6463-6466 (1992)], using expression CHO cell of prostanoide receptor subtype (mouse $EP_3\alpha$).

The standard assay mixture contained membrane fraction (0.5mg/ml), [^{3}H]-PGE_2 in a final volume of 200ml was incubated for 1 hour at room temperature. The reaction was terminated by addition of 3 ml of ice-cold buffer. The mixture was rapidly filtered through a glass filter (GF/B). The radioactivity associated with the filter was measured by liquid scintillation counting.

Kd and Bmax values were determined from Scatchard plots [Ann. N.Y. Acad. Sci., 51, 660(1949)]. Non-specific binding was calculated as the bond in the presence of an excess (2.5nM) of unlabeled PGE_2. In the experiment for competition of specific [^{3}H]-PGE_2 binding by the compounds of the present invention, [^{3}H]-PGE_2 was added at a concentration of 2.5nM and the compounds of the present invention were at a concentration of 1 mM. The following buffer was used in all reactions.

Buffer : 10mM potassium phosphate (pH6.0), 1mM EDTA, 10mM $MgCl_2$, 0.1M NaCl

The dissociation constant (Ki) of each compound was calculated by the following equation.

$$Ki = IC50/(1+([C]/Kd))$$

The results are shown in Table 50.

Table 50

Ex. No.	Ki(μM)
1	5.7
2	0.011
2a	0.11
2d	0.05
2k	0.83
2l	0.89
3	0.026
4	0.023
4a	0.20
4b	1.3
8	0.068

The toxicity of the compounds of the present invention is very low and therefore, it is confirmed that these compounds are safe for use as medicine.

The compounds of the formula (I) and non-toxic salts and hydrates thereof are useful as PGE_2 antagonists or agonists, because they bind onto prostaglandin E_2 receptors and have an antagonist or agonist activity on them.

PGE_2 antagonists are considered e.g. to inhibit uterine contraction, to have an analgesic action, to inhibit digestive peristalsis or to induce sleep; therefore they are useful for prevention and/or treatment of abortion, pain, diarrhea or insomnia.

PGE_2 agonists are considered e.g. to promote uterine contraction, to promote digestive peristalsis, to suppress gastric acid secretion or to lower blood pressure and inhibition of blood platelet aggregation as mentioned above. Therefore, PGE_2 agonists are useful as abortifacients, cathartics, and antiulcer, antigastritis, antihypertensive or antithrombosis agents.

For the purpose above described, the compounds of the formula (I), and non-toxic salts and hydrates thereof may normally be administered systemically or partially, usually by oral or parenteral administration.

The present invention provides a pharmaceutical composition which comprises a naphthyloxyacetic acid derivative of formula (I) or a non-toxic salt or hydrate thereof in association with a pharmaceutically acceptable carrier or coating.

The dose to be administered is determined depending upon e.g. age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment. In the human adult, the doses per person per dose are generally between 1 μg and 100 mg, by oral administration, up to several times per day, and between 0.1 μg and 10 mg, by parenteral administration (preferred into vein) up to several times per day, or continuous administration between 1 and 24 hrs. per day into vein.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

The compounds of the present invention may be administered in the form of e.g. solid compositions, liquid com-

positions or other compositions for oral administration, or injections, liniments or suppositories for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules.

Capsules include hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent such as lactose, mannitol, mannit, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate. The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents such as magnesium stearate, disintegrating agents such as cellulose calcium glycolate, and assisting agents for dissolving such as glutamic acid, asparaginic acid. The tablets or pills may, if desired, be coated with film of gastric or enteric material such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropyl cellulose phthalate, or be coated with two or more films. And further, coating may include containment within capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, syrups and elixirs. In such liquid compositions, one or more of the active compound(s) is or are comprised in inert diluent(s) commonly used in the art (for example, purified water or ethanol).
Besides inert diluents, such compositions may also comprise adjuvants such as wetting agents, suspending agents, sweetening agents, flavouring agents, perfuming agents and preserving agents.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents such as sodium hydrogen sulfate, stabilizing agents to give isotonicity, isotonic buffer such as sodium chloride, sodium citrate, citric acid. For preparation of such spray compositions, for example, the method described in the United States Patent No. 2868691 or 3095355 may be used.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. Aqueous solutions or suspensions include distilled water for injection and physiological salt solution. Non-aqueous solutions or suspensions may, for example, include propylene glycol, polyethylene glycol, plant oil such as olive oil, alcohol such as ethanol, or POLYSORBATE80 (registered trade mark). Such compositions may comprise additional diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agents and agents to assist dissolution (for example, glutamic acid or asparaginic acid). They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They also be manufactured in the form of sterile solid compositions and which can be dissolved in sterile water or some other sterile diluents for injection immediately before used.

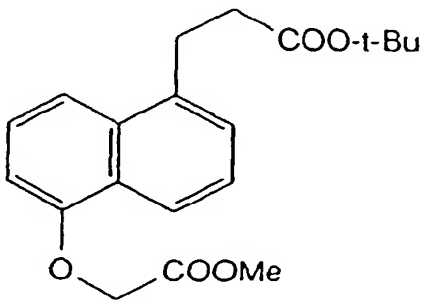
Other compositions for parenteral administration include liquids for external use, and endemic liniments, ointment, suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by known methods.

Reference Examples and Examples

The following Reference Examples and Examples illustrate the present invention. The solvents in parentheses show the developing or eluting solvents and the ratios of the solvents used are by volume in chromatographic separations. Unless otherwise specified, "NMR" spectra were measured in a solution of dimethylsulfoxide-d (DMSO-d_6).

Reference example 1"

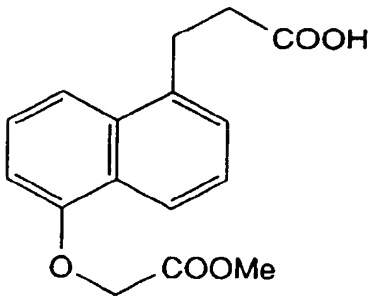
[5-(2-t-butoxycarbonylethyl)naphthyl-1-oxy]acetic acid methyl ester



The mixture of 5-(2-t-butoxycarbonylethyl)naphth-1-ol (700 mg), methyl bromoacetate (0.29ml), potassium carbonate (442 mg) and acetone (8 ml) was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified on silica gel chromatography to give the title compound (819 mg) having the following physical data.
TLC : Rf 0.34 (EtOAc:n-hexane = 1:3);
mp : 78 - 79°C.

Reference example 2

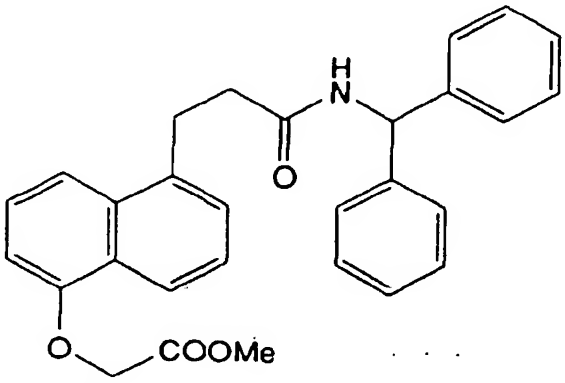
[5-(2-carboxyethyl)naphthyl-1-oxy]acetic acid methyl ester.



To a solution of the compound prepared in reference example 1 (605 mg) in dichloromethane (5 ml), trifluoroacetic acid (1 ml) was added. The mixture was stirred for 30 minutes at room temperature. The reaction solution was evaporated to dryness under reduced pressure to give the title compound (506 mg) having the following physical data.
mp : 183-185 °C.

Example 1

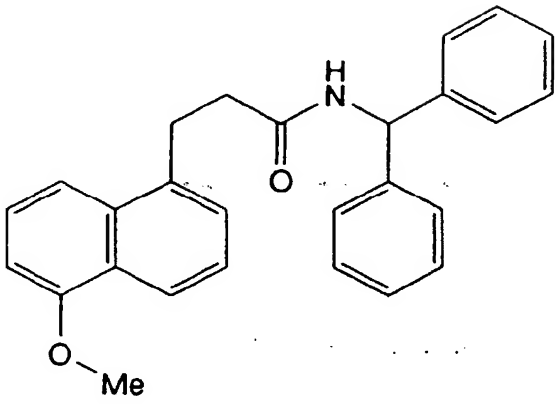
[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid methyl ester



To a solution of the compound prepared in reference example 2 (327 mg), benzhydrylamine (250 mg) and 1-ethyl-3-(dimethylaminopropyl)-carbodiimide hydrochloride salt (EDC · HCl) (261 mg) in dichloromethane (20 ml), 4-dimethylaminopyridine (14 mg) was added. The mixture was stirred for 3 days at room temperature. To the reaction solution, water was added. The mixture was extracted with ethyl acetate. The organic layer was washed with water and a saturated aqueous solution of sodium chloride, and dried over and concentrated under reduced pressure to give the title compound having the following physical data.
TLC : Rf 0.34 (EtOAc:benzene = 1:4);
NMR ($CDCl_3$) : δ 8.31 (1H, m), 7.77 (1H, d), 7.45-6.98 (13H, m), 6.71 (1H, d), 6.21 (1H, d), 5.87 (1H, d), 4.82 (2H, s), 3.82 (3H, s), 3.43 (2H, t), 2.67 (2H, t).

Example 1(a)

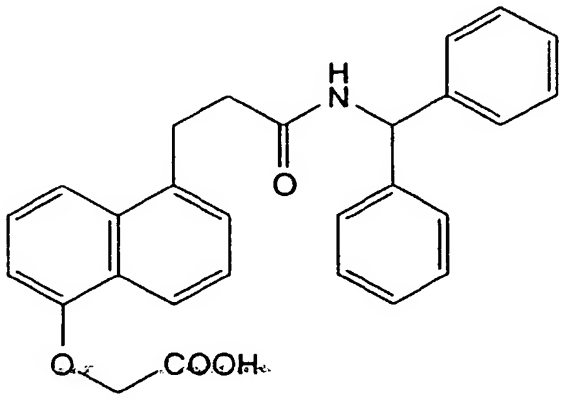
1-methoxy-5-(2-diphenylmethylaminocarbonylethyl)naphthalene



The title compound having the following physical data was obtained by the same procedure as example 1.
TLC : Rf 0.35 (n-hexane: EtOAc=2 :1);
NMR ($CDCl_3$) : δ 8.20 (1H, m), 7.61 (1H, d), 7.47-7.18 (9H, m), 7.11-6.97 (4H, m), 6.82 (1H, d), 6.21 (1H, d), 5.88 (1H, d), 4.00 (3H, s), 3.43 (2H, d), 2.67 (2H, d).

Example 2

[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid



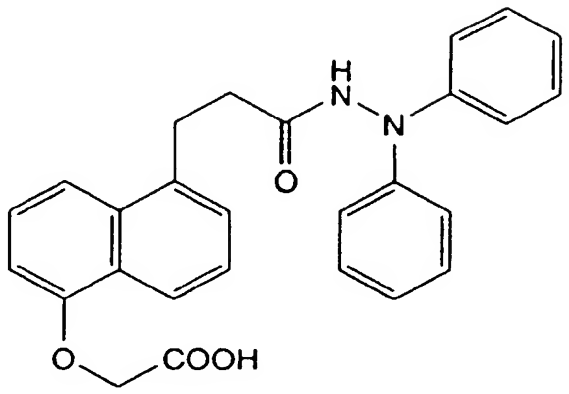
To a solution of the compound prepared in example 1 in dimethoxyethane-methanol (2:1, 10 ml), IN aqueous solution of sodium hydroxide (2 ml) was added at 0°C. Mixture was stirred for 30 minutes at room temperature. To the reaction solution, hydrochloric acid and water were added. The obtained precipitate was filtered, washed with water and ethyl acetate and dried over under reduced pressure to give the title compound (468 mg) having the following physical data.
TLC : Rf 0.08 (MeOH:CH_2Cl_2 = 1:9);
NMR : δ 8.78 (1H, d), 8.13 (1H, m), 7.67 (1H, d), 7.50-7.10 (13H, m), 6.88 (1H, d), 6.12 (1H, d), 4.87 (2H, s), 3.28 (2H, t), 2.62 (2H, t).

Example 2(a)-2(o)

The compounds having the following physical data were obtained by the same procedure as the series of reactions of reference example 1 and 2 and example 1 and 2.

Example 2(a)

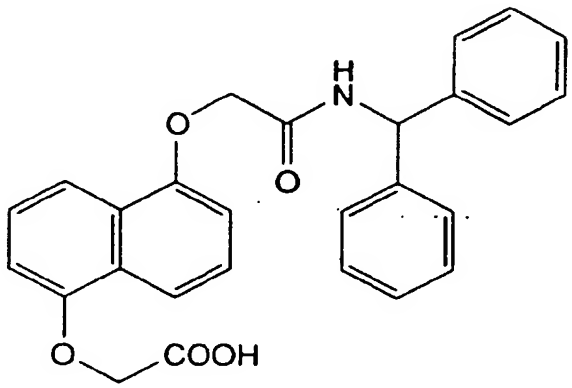
[5-[2-(3,3-diphenylcarbazoyl)ethyl]naphthyl-1-oxy]acetic acid



TLC : Rf 0.08 ($MeOH:CH_2Cl_2$ = 1:9);
NMR: δ 10.32 (1H, s), 8.04 (1H, dd), 7.56 (1H, d), 7.40-6.6 (14H, m), 4.73 (2H, s), 3.32 (2H, t), 2.48 (2H, t).

Example 2(b)

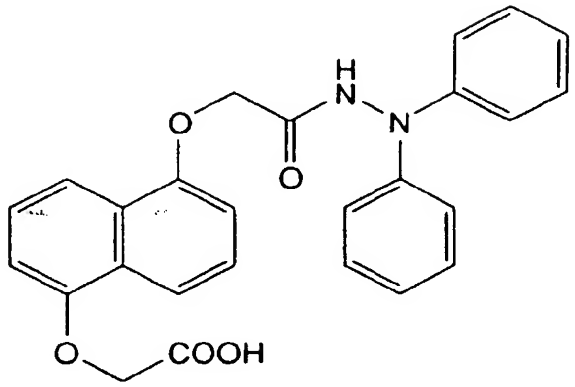
[5-(diphenylmethylaminocarbonylmethoxy)naphthyl-1-oxy]acetic acid



TLC : Rf 0.51 ($MeOH:CH_2Cl_2$ = 1:4);
NMR: δ 9.09 (1H, d), 7.82 (2H, d), 7.5-7.2 (12H, m), 6.92 (1H, d), 6.91 (1H, d), 6.21 (1H, d), 4.85 (2H, s), 4.83 (2H, s), 3.35 (1H, br).

Example 2(c)

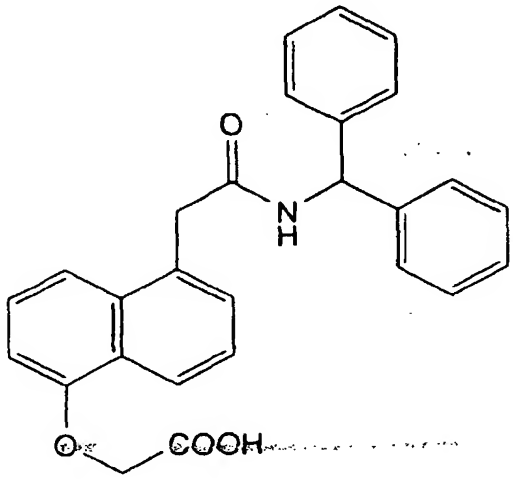
[5-[(3, 3-diphenylcarbazoyl)methoxy]naphthyl-1-oxy]acetic acid



TLC : Rf 0.46 ($MeOH:CH_2Cl_2$ = 1:4);
NMR : δ 10.96 (1H, s), 7.98 (1H, d), 7.86 (1H, d), 7.44 (1H, t), 7.42 (1H, t), 7.28 (4H, t), 7.12 (4H, d), 7.1-6.9 (4H, m), 4.90 (2H, s), 4.87 (2H, s), 3.34 (1H, br).

Example 2(d)

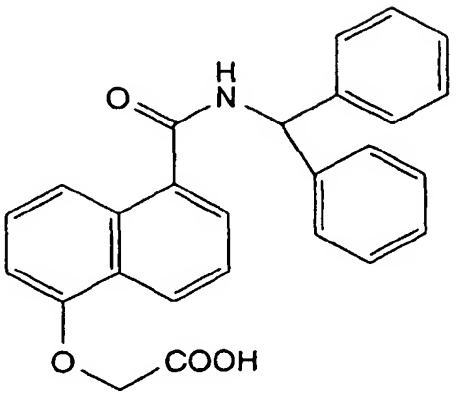
[5-(diphenylmethylaminocarbonylmethyl)naphthyl-1-oxy]acetic acid



TLC : Rf 0.35 ($MeOH:CHCl_3$ = 3:7);
NMR : δ 13.00 (1H, brs), 9.17 (1H, d), 8.17 (1H, dd), 7.70 (1H, d), 7.50-7.17 (13H, m), 6.87 (1H, d), 6.12 (1H, d), 4.86 (2H, s), 4.02 (2H, s).

Example 2(e)

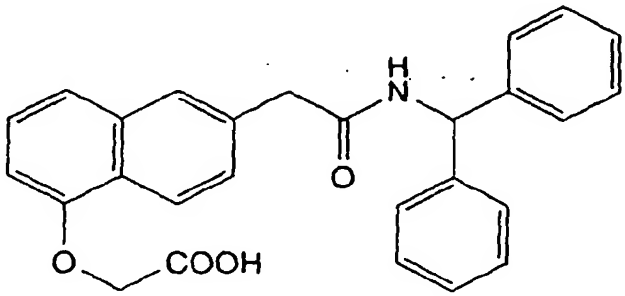
[5-(diphenylmethylaminocarbonyl)naphthyl-1-oxy]acetic acid



TLC . Rf 0.19 ($MeOH:CH_2Cl_2$ = 1:5);
NMR ($CDCl_3$+CD_3OD) : δ 8.40 (1H, d), 8.29 (1H, s), 7.87 (1H, d), 7.53 (1H, d), 7.48-7.20 (11H, m), 6.82 (1H, d), 6.50 (1H, s), 4.80 (2H, s).

Example 2(f)

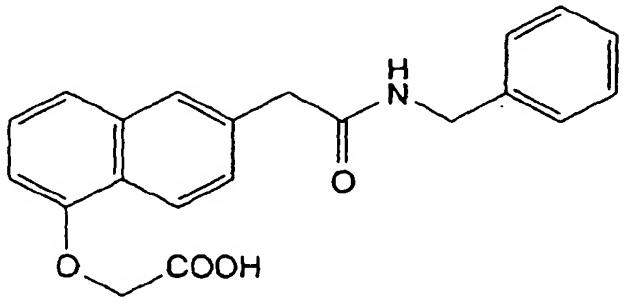
[6-(diphenylmethylaminocarbonylmethyl)naphthyl-1-oxy]acetic acid



TLC : Rf 0.30 ($MeOH:CH_2Cl_2$ = 1:4);
NMR : δ 9.10 (1H, d), 8.13 (1H, d), 7.72 (1H, s), 7.52-7.17 (13H, m), 6.82 (1H, dd), 6.13 (1H, d), 4.86 (2H, s), 3.73 (2H, s).

Example 2(g)

[6-(phenylmethylaminocarbonylmethyl)naphthyl-1-oxy]acetic acid

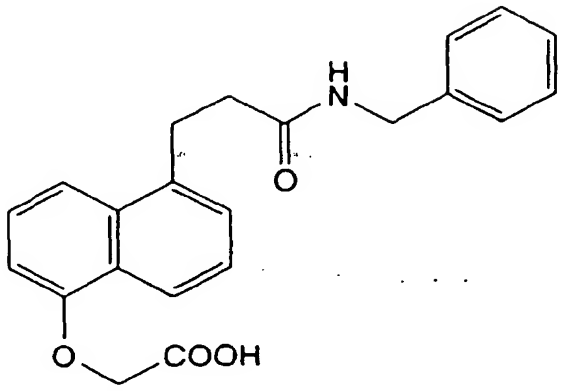


TLC : Rf 0.23 ($MeOH:CH_2Cl_2$ = 1:4);

NMR: δ 8.61 (1H, t), 8.15 (1H, d), 7.73 (1H, s), 7.50-7.13 (8H, m), 6.84 (1H, d), 4.87 (2H, s), 4.30 (2H, d), 3.67 (2H, s).

Example 2(h)

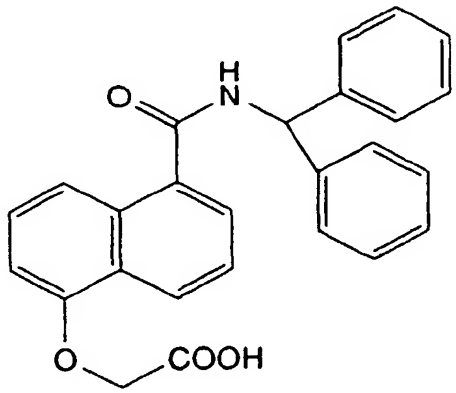
[5-(2-phenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid



TLC : Rf 0.28 ($MeOH:CHCl_3$ = 3:7);
NMR($DMSO\text{-}d6+CDCl_3$) : δ 8.27-8.12 (2H, m), 7.69 (1H, d), 7.48-7.10 (8 H, m), 6.79 (1H, d), 4.79 (2H, s), 4.30 (2H, d), 3.35 (2H, t), 2.60 (2H, t).

Example 2(i)

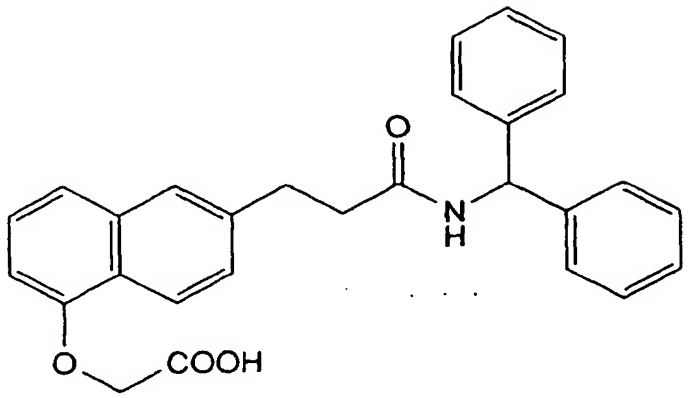
[5-(diphenylmethylaminocarbonyl)naphthyl-1-oxy]acetic acid



TLC : Rf 0.15 ($MeOH:CH_2Cl_2$ = 1:5);
NMR ($CDCl_3+CD_3OD$) : δ 8.49 (1H, d), 7.78 (1H, d), 7.65 (1H, d), 7.53-7.20 (12H, m), 6.79 (1H, d), 6.54 (1H, s), 4.79 (2H, s).

Example 2(j)

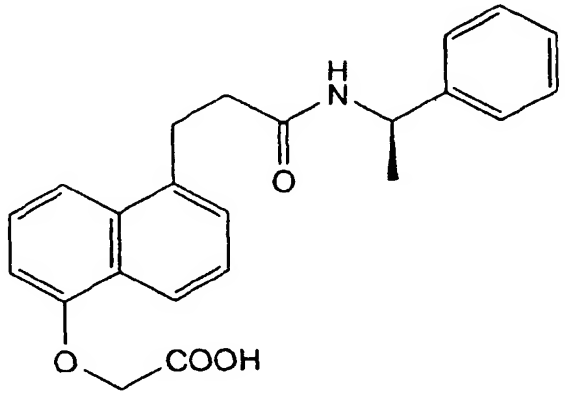
[6-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid



TLC : Rf 0.30 ($MeOH:CHCl_3$ = 3:7);
NMR: δ 8.77 (1H, d), 8.13 (1H, d), 7.66 (1H, s), 7.43-7.06 (13H, m), 6.83 (1H, m), 6.09 (1H, d), 4.90 (2H, s), 3.03 (2H, t), 2.64 (2H, t).

Example 2(k)

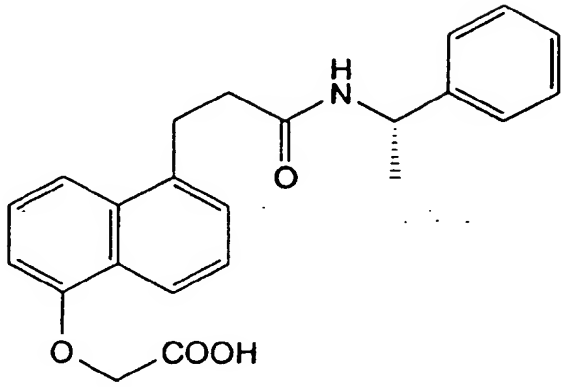
[5-[2-((1R)-1-phenylethyl)aminocarbonylethyl]naphthyl-1-oxy]acetic acid



TLC : Rf 0.21 ($CHCl_3$:MeOH = 20:1);
NMR : δ 13.18-12.92 (1H, br), 8.30 (1H, d), 8.18 (1H, d), 7.63 (1H, d), 7.40-7.18 (8H, m), 6.89 (1H, d), 5.00-4.89 (1H, m), 4.88 (2H, s), 3.31-3.22 (2H, m), 2.52-2.49 (2H, m), 1.31 (3H, d).

Example 2(l)

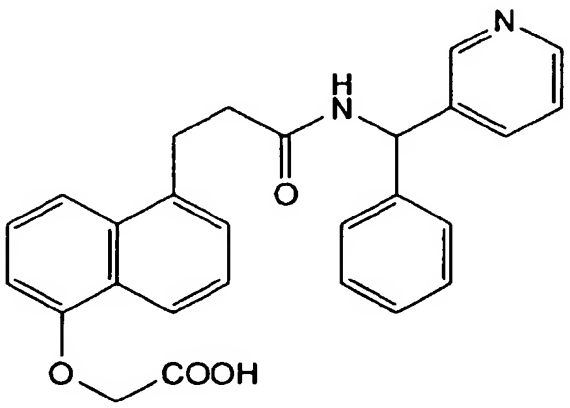
[5-[2-((1S)-1-phenylethyl)aminocarbonylethyl]naphthyl-1-oxy]acetic acid



TLC : Rf 0.21 ($CHCl_3$:MeOH = 20:1);
NMR : δ 13.18-12.92 (1H, br), 8.30 (1H, d), 8.18 (1H, d), 7.63 (1H, d), 7.40-7.18 (8H, m), 6.89 (1H, d), 5.00-4.89 (1H, m), 4.88 (2H, s), 3.31-3.22 (2H, m), 2.52-2.49 (2H, m), 1.31 (3H, d).

Example 2(m)

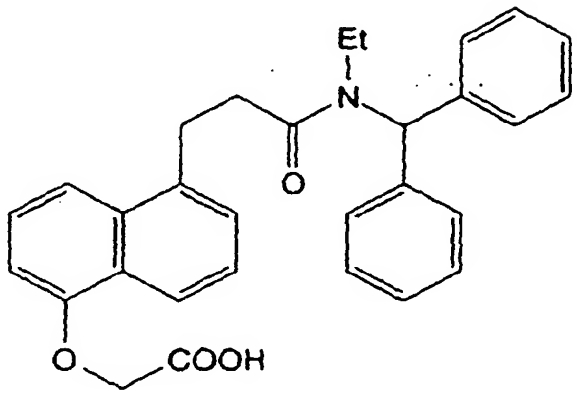
[5-[2-[1-phenyl-1-(3-pyridyl)methyl]aminocarbonylethyl]naphthyl-1-oxy]acetic acid



TLC : Rf 0.22 ($CHCl_3$:MeOH = 20:1);
NMR: δ 8.82 (1H, d), 8.17 (1H, d), 7.61 (1H, d), 7.40-7.18 (13H, m), 6.75 (1H, d), 6.14 (1H, d), 4.34 (2H, s), 2.59 (2H, t), 2.50-2.49 (2H, m).

Example 2(n)

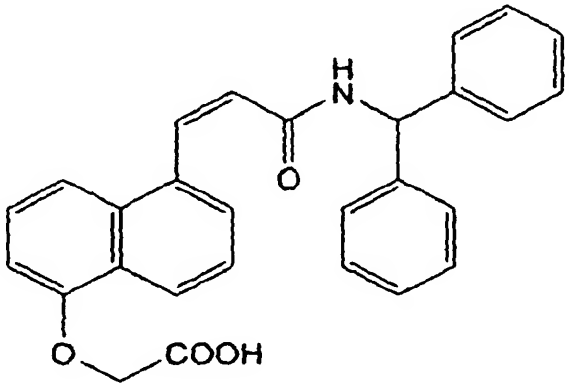
[5-[2-(N-diphenylmethyl-N-ethylaminocarbonyl)ethyl]naphthyl-1-oxy]acetic acid



TLC : Rf 0.28 ($CHCl_3$:MeOH = 20:1);
NMR: δ 8.12-7.99 (2H, m), 7.39-7.06 (8H, m), 6.99-6.95 (4H, m), 6.85-6.59 (2H, m), 4.45 (2H, s), 3.94-3.38 (4H, m), 2.81-2.59 (2H, m), 0.46-0.18 (3H, m).

Example 2(o)

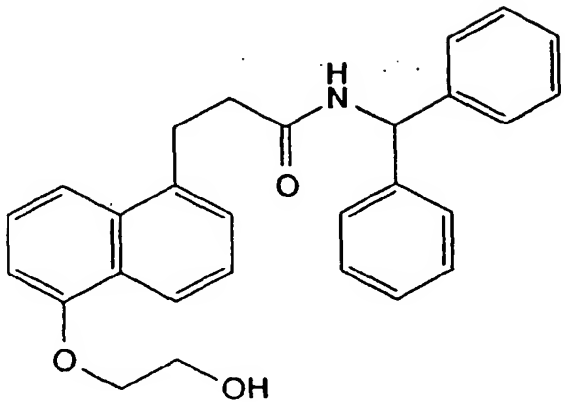
[5-[2-(diphenylmethylaminocarbonyl)vinyl]naphtyl-1-oxy]acetic acid



TLC : 0.50 ($CHCl_3$:MeOH:AcOH = 93:5:2);
NMR: δ 9.15 (1H, d), 8.32 (1H, d), 8.23 (1H, d), 7.81 (1H, d), 7.76 (1H, d), 7.57 (1H, dd), 7.50 (1H, dd), 7.40-7.20 (10H, m), 6.96 (1H, d), 6.92 (1H, d), 6.32 (1H, d), 4.89 (2H, s).

Example 3

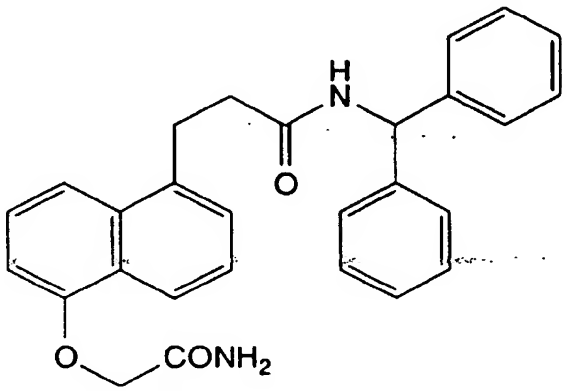
2-[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]ethanol



To a solution of the compound prepared in example 1 (750 mg) in methanol-THF (10 ml+6ml), sodium boro hydride (125 mg) was added. The mixture was stirred for 2 hours at 60°C. After termination of reaction, IN hydrochloric acid was added to the reaction mixture. The mixture was extracted with methylene chloride. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over and concentrated under reduced pressure. The residue was purified on silica gel chromatography to give the title compound (600 mg) having the following physical data:
TLC : Rf 0.40 (EtOH : CH_2Cl_2=3 : 7);
NMR($CDCl_3$) : δ 8.21 (1H, m), 7.65 (1H, d, J=8Hz), 7.45-7.17 (9H, m), 7.13-6.98 (4H, m), 6.85 (1H, d, J=8Hz); 6.22 (1H, d, J=8Hz), 5.86 (1H, d, J=8Hz), 4.28 (2H, t, J=4Hz), 4.12 (2H, m), 3.45 (2H, t, J=7Hz), 2.68 (2H, t, J=7Hz), 2.14 (1H, t, J=7Hz).

Example 4

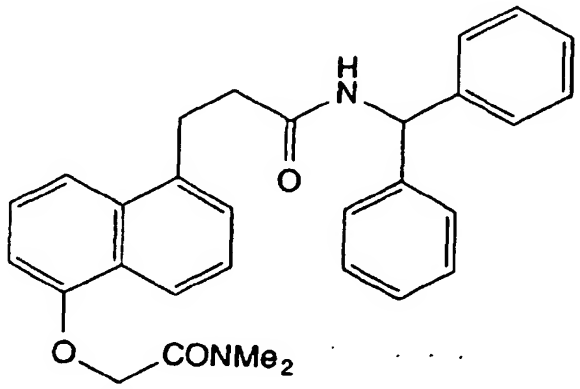
[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid amide



To a solution of the compound prepared in example 1 (75 mg) in THF (1 ml), conc. aqueous solution of ammonia (0.2 ml) was added. The mixture was stirred for 10 hours at room temperature. The reaction solution was diluted with methylene chloride, washed with 1N hydrochloric acid and a saturated aqueous solution of sodium chloride, dried over and concentrated under reduced pressure. The residue was purified on silica gel chromatography to give the title compound having the following physical data:
TLC : Rf 0.46 ($CHCl_3$: MeOH=9 : 1);
NMR: δ 8.79 (1H, d, J=9Hz), 8.28 (1H, m), 7.69 (1H, d, J=9Hz), 7.64-7.14 (15H, m), 6.90 (1H, d, J=7Hz), 6.13 (1H, d, J=9Hz), 4.62 (2H, s), 3.32 (2H, m), 2.63 (2H, t, J=8Hz).

Example 4(a)

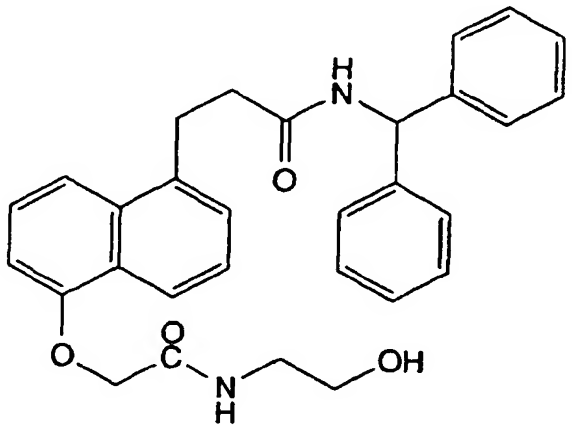
N,N-dimethyl-[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid amide



The title compound having the following physical data was obtained by the same procedure as example 4.
TLC : Rf 0.58 ($CHCl_3$: MeOH=9 : 1);
NMR($CDCl_3$) : δ 8.22 (1H, m), 7.64 (1H, d, J=8Hz), 7.43-7.16 (9H, m), 7.12-7.00 (4H, m), 6.83 (1H, d, J=8Hz), 6.22 (1H, d, J=8Hz), 6.08 (1H, d, J=8Hz), 4.83 (2H, s), 3.42 (2H, t, J=8Hz), 3.12 (3H, s), 2.97 (3H, s), 2.66 (2H, t, J=8Hz).

Example 4(b)

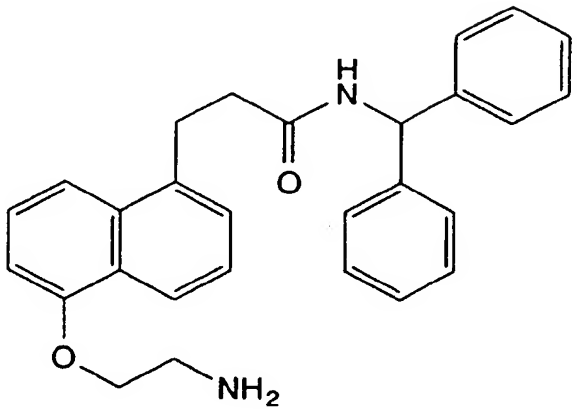
N-(2-hydroxyethyl)-[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid amide



The title compound having the following physical data was obtained by the same procedure as example 4.
TLC : Rf 0.44 ($CHCl_3$: MeOH=9 : 1);
NMR ($CDCl_3$) : δ 8.14 (1H, m), 7.72 (1H, d, J=9Hz), 7.50-7.34 (3H, m), 7.34-7.18 (6H, m), 7.14-6.98 (5H, m), 6.82 (1H, d, J=7Hz), 6.22 (1H, d, J=8Hz), 5.89 (1H, d, J=8Hz), 4.71 (2H, s), 3.77 (2H, m), 3.56 (2H, t, J=5Hz), 3.46 (2H, t, J=8Hz), 2.69 (2H, t, J=8Hz), 2.24 (1H, t, J=5Hz).

Example 5

2-[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]ethylamine



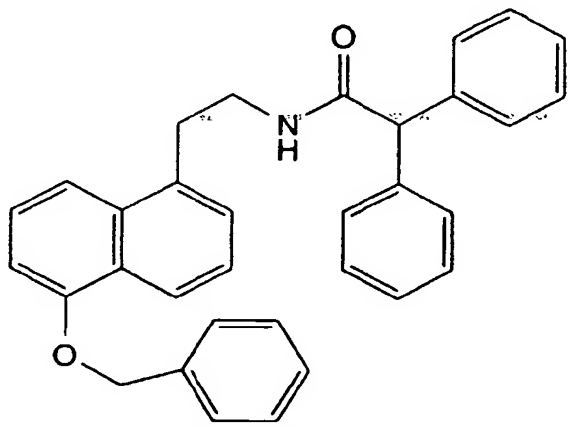
To a solution of compound prepared in example 3 (51 mg) in pyridine (1 ml), tosyl chloride (30 mg) was added. The mixture was stirred for 1 hour at room temperature. The reaction solution was diluted with methylene chloride, washed with 1N hydrochloric acid, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over and concentrated under reduced pressure. To a solution of the residue (65 mg) in dimethylformamide (DMF), sodium azide (16 mg) was added. The mixture was refluxed with heating for 4 hours. After cooling the reaction mixture, the reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, dried over and concentrated under reduced pressure. To a solution of the residue (48 mg) in methanol (2 ml), Pd-C (10 mg; 10%) was added. The mixture was stirred under an atmosphere of hydrogen gas for 1 night at room temperature. Reaction solution was filtered and concentrated under reduced pressure. The residue was purified on silica gel chromatography to give the title compound (31 mg) having the following physical data.

TLC : Rf 0.28 (MeOH : $CHCl_3$ = 3 : 7);

NMR ($CDCl_3$): δ 8.20 (1H, m), 7.62 (1H, d, J=8Hz), 7.43-6.97 (13H, m), 6.81 (1H, d, J=8Hz), 6.21 (1H, d, J=8Hz), 6.01 (1H, d, J=8Hz), 4.14 (2H, t, J=5Hz), 3.45 (2H, t, J=7Hz), 3.19 (2H, t, J=5Hz), 2.67 (2H, t, J=7Hz), 1.50 (2H, s).

Reference example 3

1-benzyloxy-5-[2-(diphenylmethylcarbonylamino)ethyl]naphthalene

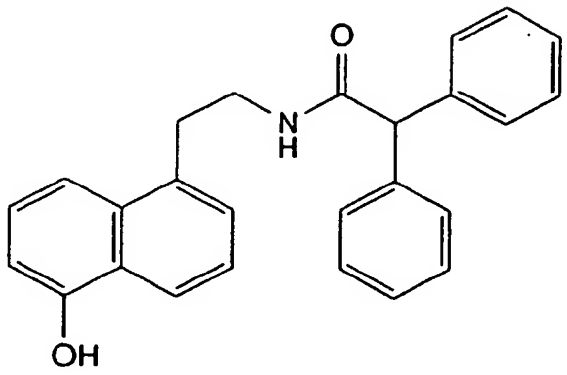


To a solution of diphenylacetic acid (0.171 g) in methylene chloride (10 ml), dimethylaminopyridine (0.01g) and 1-benzyloxy-5-(2-aminoethyl)naphthalene (0.196 g) were added at room temperature. After 10 minutes, EDC · HCl (0.154 g) was added to the mixture solution. The mixture was stirred overnight at room temperature for 1 night. After termination of reaction, water and methylene chloride were added to the reaction mixture. The organic layer was washed with a saturated aqueous solution of ammonium chloride, water and a saturated aqueous solution of sodium chloride,

dried over and concentrated under reduced pressure. The residue was purified on silica gel chromatography to give the title compound (0.172 g) having the following physical data.
TLC : Rf 0.42 (EtOAC : n-hexane = 1:2).

Example 6

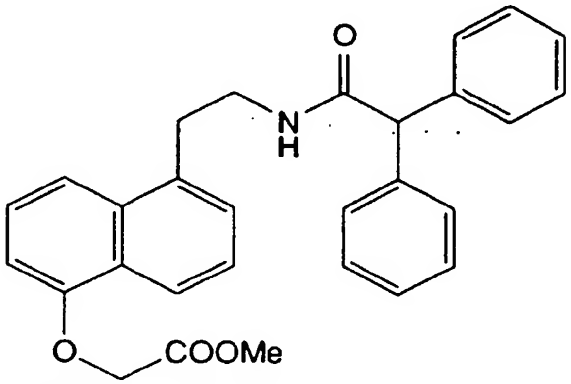
5-[2-(diphenylmethylcarbonylamino)ethyl]naphth-1-ol



Under an atmosphere of hydrogen gas, the mixture of the compound prepared in reference example 3 (0.168 g), Pd-C (0.1 g; 10%) and methanol (20 ml) was stirred vigorously for 3 hours at room temperature. The reaction mixture was filtered and concentrated under reduced pressure to give the title compound (0.13 g) having the following physical data.
TLC : Rf 0.26 (EtOAC : n-hexane = 1:2).

Example 7

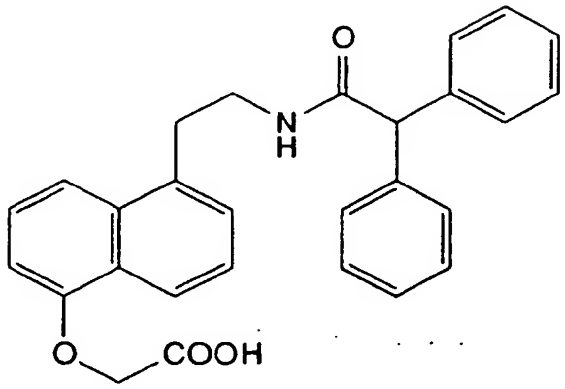
[5-[2-(diphenylmethylcarbonylamino)ethyl]naphthyl-1-oxy]acetic acid methyl ester



To a solution of the compound prepared in example 6 (0.128 g) in acetone (15 ml), potassium carbonate (0.056 g) and methyl bromoacetate (0.062 g) were added at room temperature. The reaction solution was stirred for overnight at room temperature. The reaction solution was filtered and concentrated under reduced pressure. The residue was purified by recrystalization from ethyl acetate-hexane solvent to give the title compound (0.073 g) having the following physical data.
TLC : Rf 0.48 (EtOAc : benzene = 1:5).

Example 8

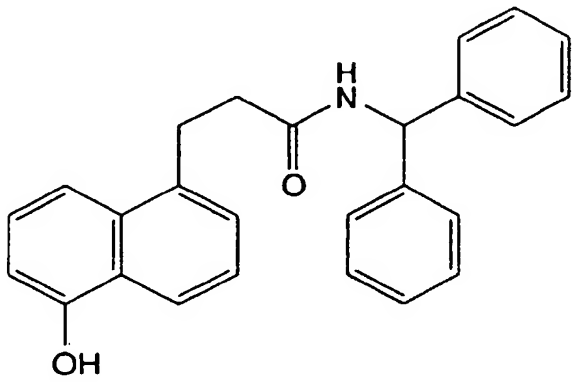
[5-[2-(diphenylmethylcarbonylamino)ethyl]naphthyl-1-oxy]acetic acid



By using the compound prepared in example 7 (0.067 g), the title compound (0.05 g) having the following physical data was obtained by the same procedure as example 2.
TLC : Rf 0.22 (MeOH :CH_2Cl_2 = 1:5);
NMR ($CDCl_3$+CD_3OD) : δ 826 (1H, d), 7.65 (1H, d), 7.40-7.00 (13H, m), 6.75 (1H, d), 627-6.10 (1H, m), 4.85 (1H, s), 4.80 (2H, s), 3.80-3.40 (2H, m), 3.22 (2H, t).

Example 9

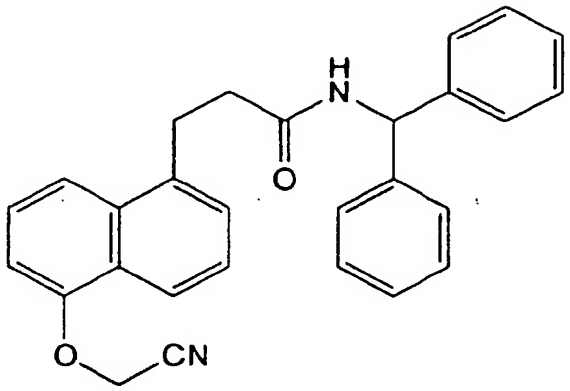
5-(2-diphenylmethylaminocarbonylethyl)naphth-1-ol



To a solution of the compound prepared in example 1(a) in methylene chloride (50 ml), BBr_3 (0.96 ml) was added dropwise at 0°C. The reaction solution was stirred for 30 minutes at room temperature. The reaction solution was poured into iced water and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium hydrogecarbonate and a saturated aqueous solution of sodium chloride, dried over and concentrated under reduced pressure. The residue was purified by recrystalization (ethyl acetate-hexane) to give the title compound (1.62 g) having the following physical data.
TLC : Rf 0.20 (n-hexane : EtOAc = 2 : 1);
NMR : δ 10.07 (1H, s), 8.79 (1H, d), 8.05 (1H, m), 7.53 (1H, d), 7.40-7.16 (13H, m), 6.88 (1H, d), 6.14 (1H, d), 3.38 (2H, d), 2.63 (2H, d).

Example 10

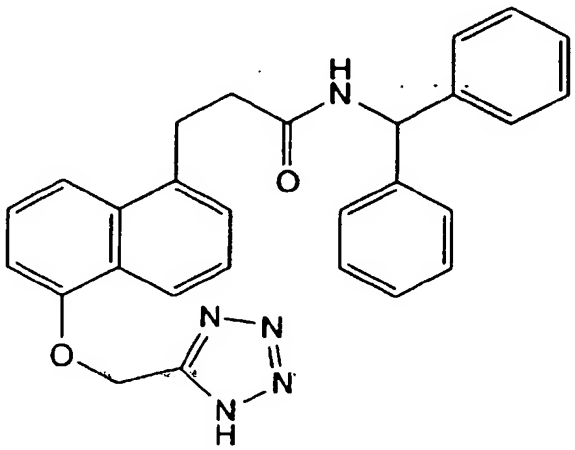
1 -cyanomethoxy-5-(2-diphenylmethylaminocarbonylethyl)naphthalene



By using the compound prepared in example 9, the title compound having the following physical data was obtained by the same procedure as example 7.
TLC : Rf 0.30 (n-hexane:EtOAc = 7:3);
NMR ($CDCl_3$) : δ 8.12 (1H, t-like), 7.77 (1H, d), 7.46 (1H, d), 7.41-7.38 (2H, m), 7.29-7.24 (6H, m), 7.07-7.03 (4H, m), 6.93 (1H, d), 6.21 (1H, d), 5.92-5.79 (1H, m), 4.97 (3H, s), 3.46 (2H, t), 2.68 (2H, t).

Example 11

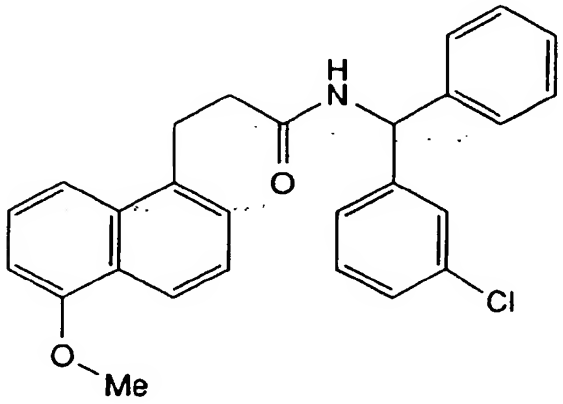
1-tetrazolylmethoxy-5-(2-diphenylmethylaminocarbonylethyl)naphthalene



To a solution of the compound prepared in example 10 (420 mg) in DHF (2 ml), sodium azido (72 mg) and ammonium chloride (59 mg) were added. The mixture was stirred for 12 hours at 120°C. To the reaction solution, water (2 ml) was added. The mixture solution was adjusted to pH2 by adding conc. hydrochloric acid. The obtained precipitate was collected with filter, washed with iced water and ether and dried over under reduced pressure to give the title compound (391 mg) having the following physical data.
TLC : Rf 0.31 ($CHCl_3$: MeOH = 20:1);
NMR : δ 8.67 (1H, d), 8.03 (1H, t-like), 7.58 (1H, d), 7.37 (1H, d), 7.29-6.89 (13H, m), 6.00 (1H, d), 5.56 (3H, s), 3.17 (2H, t), 2.51 (3H, t).

Example 12

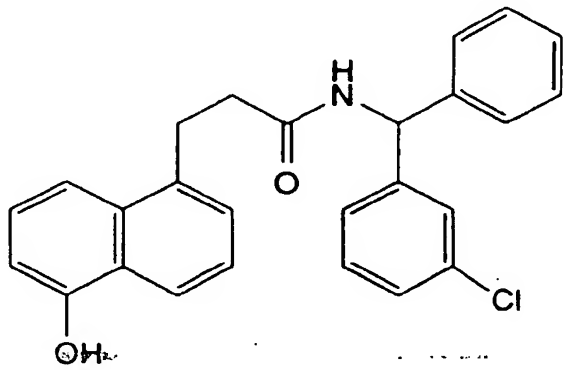
1-methoxy-5-[2-[1-phenyl-1-(3-chlorophenyl)methyl]aminocarbonylethyl]naphthalene



By using [1-phenyl-1-(3-chlorophenyl)methyl]amine instead of benzhydrylamine in example 1, the title compound having the following physical data was obtained by the same procedure as example 1.
TLC : Rf 0.50 (n-hexane: EtOAc=1:1);
NMR ($CDCl_3$) : δ 8.20 (1H, m), 7.62 (1H, d), 7.52-6.80 (13H, m), 6.16 (1H, d), 5.80 (1H, d), 4.02 (3H, s), 3.45 (2H, t), 2.69 (2H, t).

Example 13

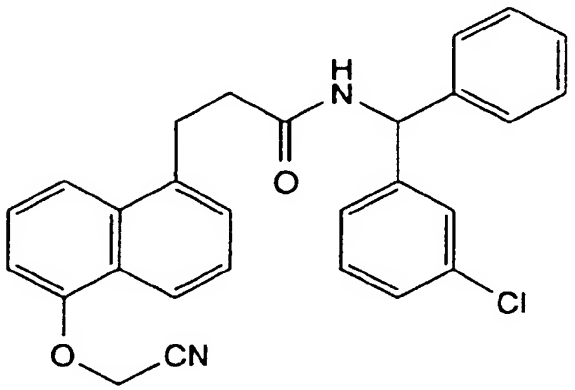
5-[2-[1-phenyl-1-(3-chlorophenyl)methyl]aminocarbonylethyl]naphth-1-ol



By using the compound prepared in example 12, the title compound having the following physical data was obtained by the same procedure as example 9.
TLC : Rf 0.41 (n-hexane : EtOAc= 1:1);
NMR : δ 10.05 (1H, s), 8.82 (1H, d), 8.03 (1H, m), 7.52 (1H, d), 7.40-7.15 (12H, m), 6.88 (1H, d), 6.15 (1H, d), 3.27 (2H, t), 2.63 (2H, t).

Example 14

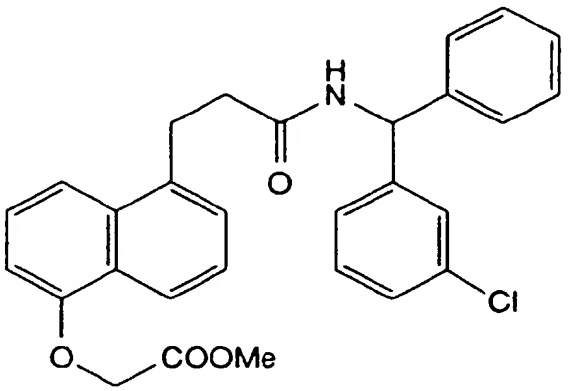
1 -cyanomethoxy-5-[2-[1-phenyl-1-(3-chlorophenyl)methyl]aminocarbonylethyl]naphthalene



By using the compound prepared in example 13, the title compound having the following physical data was obtained by the same procedure as example 7.
TLC : Rf 0.30 (EtOAC : benzene = 3 : 17);
NMR ($CDCL_3$) : δ 8.13 (1H, m), 7.76 (1H, d, J=8Hz),7.52-6.86 (13H, m), 6.16 (1H, d, J=8Hz), 5.90 (1H, d, J=8Hz, NH), 4.97 (2H, s, $-OCH_2$), 3.44 (2H, t, J=7Hz), 2.67 (2H, t, J=7Hz).

Example 15

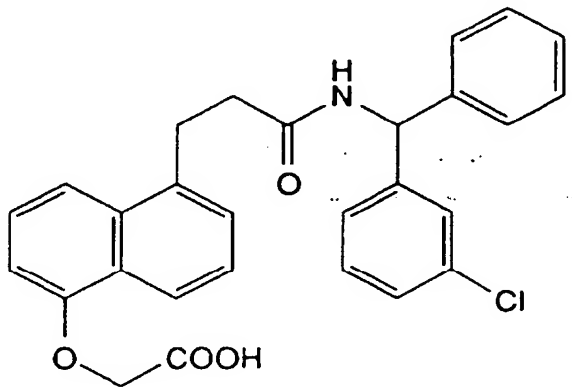
[5-[2-[1 -phenyl-1-(3-chlorophenyl)methyl]aminocarbonylethyl]naphthyl-1-oxy]acetic acid methyl ester



By using the compound prepared in example 13, the title compound having the following physical data was obtained by the same procedure as example 7.
TLC : Rf 0.33 (EtOAc : benzene = 3 : 17);
NMR ($CDCl_3$) : δ 8.27 (1H, m), 7.67 (1H, d, J=8Hz), 7.50-6.87 (12H, m), 6.71 (1H, d, J=8Hz), 6.16 (1H, d, J=8Hz), 5.83 (1H, d, J=8Hz, NH), 4.82 (2H, s, $-OCH_2$), 3.83 (3H, s, $-OCH_3$), 3.44 (2H, t, J=7Hz), 2.67 (2H, t, J=7Hz).

Example 16

[5-[2-[1-phenyl-1-(3-chlorophenyl)methyl]aminocarbonylethyl]naphthyl-1-oxy]acetic acid



By using the compound prepared in example 15, the title compound having the following physical data was obtained by the same procedure as example 2.
TLC : Rf 0.18 ($MeOH:CHCl_3$=1:4);
NMR : δ 13.07 (1H, brs, COOH), 8.82 (1H, d, J=8Hz, NH), 8.13 (1H, m), 7.67 (1H, d, J=8Hz), 7.50-7.11 (12H, m), 6.87 (1H, d, J=8Hz), 6.15 (1H, d, J=8Hz), 4.86 (2H, s, $-OCH_2$), 3.30 (2H, t, J=7Hz), 2.63 (2H, t, J=7Hz).

[Formulation example]

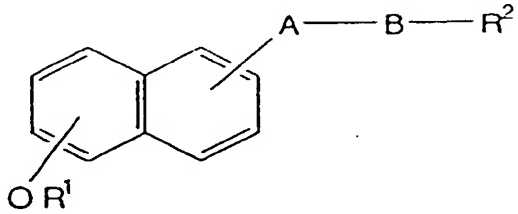
Formulation example 1:

The following compounds were admixed in conventional method and punched out to obtain 100 tablets each containing 5 mg of active ingredient.

- [5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1 -oxy]acetic acid methyl ester (compound of example 1) 500 mg
- Carboxymethylcellulose calcium 200 mg
- Magnesium stearate 100 mg
- Micro crystalline cellulose 9.2 g

Claims

1. A naphthyloxyacetic acid derivative of the formula (I)



(I)

wherein

R^1 is

(i) hydrogen,
(ii) C1-4 alkyl,
(iii) (C1-4 alkylene)-$COOR^{10}$ in which R^{10} is hydrogen or C1-4 alkyl,
(iv) (C1-4 alkylene)-OH,

(v) (C1-4 alkylene)-CONR^{4}R^5 in which R^4 and R^5 each, independently, is hydrogen or C1-4 alkyl,
(vi) (C1-4 alkylene)-CONR6-(C1-4 alkylene)-OH in which R^6 is hydrogen or C1-4 alkyl,
(vii) (C1-4 alkylene)-NR^{4}R^5 in which R^4 and R^5 are as hereinbefore defined,
(viii) (C1-4 alkylene)-cyano or
(ix) (C1-4 alkylene)-tetrazolyl,

A is a single bond, C1-6 alkylene, C2-6 alkenylene, -S-(C1-6 alkylene) or -O-(C1-6 alkylene),
B is NR^{3}CO or CONR^3, in which, R^3 is hydrogen or C1-4 alkyl, and
R^2 is

(i) C1-6 alkyl,
(ii) C2-6 alkenyl,
(iii) C1-6 alkyl substituted by 1-3 substituent(s) selected from phenyl, C4-7 cycloalkyl, naphthyl and 4-7 membered heterocyclic ring containing one nitrogen atom,
(iv) C2-6 alkenyl substituted by 1-3 substituent(s) selected from phenyl, C4-7 cycloalkyl, naphthyl and 4-7 membered heterocyclic ring containing one nitrogen atom,
(v) NR^{7}R^8 in which R^7 and R^8 each, independently, is phenyl, C4-7 cycloalkyl, naphthyl or 4-7 membered heterocyclic ring containing one nitrogen atom or
(vi) (C1-6 alkylene)-NR^{7}R^8 in which R^7 and R^8 are as hereinbefore defined,

and, when R^2 contains a phenyl, cycloalkyl, naphthyl or heterocyclic ring, said ring is unsubstituted or substituted by 1-3 substituent(s) selected from C1-4 alkyl, C1-4 alkoxy, halogen, nitro and trifluoromethyl; or a non-toxic salt, non-toxic acid addition salt or hydrate thereof.

2. A compound according to claim 1, wherein R^1 is (C1-4 alkylene)-COOR^{10}.

3. A compound according to claim 1, wherein R^1 is hydrogen, C1-4 alkyl, (C1-4 alkylene)-OH, (C1-4 alkylene)-CONR^{4}R^5, (C1-4 alkylene)-CONR^6-(C1-4 alkylene)-OH, (C1-4 alkylene)-NR^{4}R^5, (C1-4 alkylene)-cyano or (C1-4 alkylene)-tetrazolyl.

4. A compound according to any one of claims 1 to 3, wherein R^2 is

(i) C1-6 alkyl,
(ii) C2-6 alkenyl,
(iii-a) C1-6 alkyl substituted by 1-3 substituent(s) selected from phenyl, C4-7 cycloalkyl and naphthyl,
(iv-a) C2-6 alkenyl substituted by 1-3 substituent(s) selected from phenyl, C4-7 cycloalkyl and naphthyl,
(v-a) NR^{7a}R^{8a} in which R^{7a} and R^{8a} each, independently, is phenyl, C4-7 cycloalkyl or naphthyl or
(vi-a) (C1-6 alkylene)-NR^{7a}R^{8a} in which R^{7a} and R^{8a} are as hereinbefore defined.

5. A compound according to any one of claims 1 to 3, wherein R^2 is

(iii-b) C1-6 alkyl substituted by one 4-7 membered heterocyclic ring containing one nitrogen atom, said alkyl having no additional substituents or having one or two additional substituents selected from phenyl, C4-7 cycloalkyl, naphthyl and 4-7 membered heterocyclic ring containing one nitrogen atom,
(iv-b) C2-6 alkenyl substituted by one 4-7 membered heterocyclic ring containing one nitrogen atom, said alkenyl having no additional substituents or having one or two additional substituents slected from phenyl, C4-7 cycloalkyl, naphthyl and 4-7 membered heterocyclic ring containing one nitrogen atom,
(v-b) NR^{7b}R^{8b} in which one of R^{7b} and R^{8b} is phenyl, C4-7 cycloalkyl, naphthyl or 4-7 membered heterocyclic ring containing one nitrogen atom and the other is 4-7 membered heterocyclic ring containing one nitrogen atom or
(vi-b) (C1-6 alkylene)-NR^{7b}R^{8b} in which R^{7b} and R^{8b} are as hereinbefore defined.

6. A compound according to claim 4, which is

[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid,
[5-[2-(3,3-diphenylcarbazoyl)ethyl]naphthyl-1-oxy]acetic acid,
[5-(diphenylmethylaminocarbonylmethoxy)naphthyl-1-oxy]acetic acid,

[5-[(3,3-diphenylcarbazoyl)methoxy]naphthyl-1-oxy]acetic acid,
[5-(diphenylmethylaminocarbonylmethyl)naphthyl-1-oxy]acetic acid,
[5-(diphenylmethylaminocarbonyl)naphthyl-1-oxy]acetic acid,
[6-(diphenylmethylaminocarbonylmethyl)naphthyl-1-oxy]acetic acid,
[6-(phenylmethylaminocarbonylmethyl)naphthyl-1-oxy]acetic acid,
[5-(2-phenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid,
[5-(diphenylmethylaminocarbonyl)naphthyl-1-oxy]acetic acid,
[6-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid,
[5-[2-((1R)-1-phenylethyl)aminocarbonylethyl]naphthyl-1-oxy]acetic acid,
[5-[2-((1S)-1-phenylethyl)aminocarbonylethyl]naphthyl-1-oxy]acetic acid,
[5-[2-(N-diphenylmethyl-N-ethylaminocarbonyl)ethyl]naphthyl-1-oxy]acetic acid,
[5-[2-(diphenylmethylaminocarbonyl)vinyl]naphthyl-1-oxy]acetic acid,
[5-[2-(diphenylmethylcarbonylamino)ethyl]naphthyl-1-oxy]acetic acid or
[5-[2-[1-phenyl-1-(3-chlorophenyl)methyl]aminocarbonylethyl]naphthyl-1-oxy]acetic acid or the methyl ester thereof.

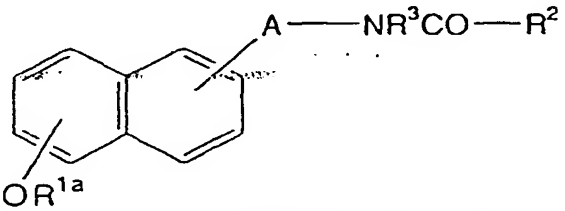
7. A compound according to claim 5, which is [5-[2-[1-phenyl-1-(3-pyridyl)methyl]aminocarbonylethyl]naphthyl-1-oxy] acetic acid or the methyl ester thereof.

8. A compound according to claim 3, which is

1 -methoxy-5-(2-diphenylmethylaminocarbonylethyl)naphthalene,
2-[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]ethanol,
[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid amide,
N,N-dimethyl-[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid amide,
N-(2-hydroxyethyl)-[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]acetic acid amide,
2-[5-(2-diphenylmethylaminocarbonylethyl)naphthyl-1-oxy]ethylamine
5-[2-(diphenylmethylcarbonylamino)ethyl]naphth-1-ol,
5-(2-diphenylmethylaminocarbonylethyl)naphth-1-ol,
1-cyanomethoxy-5-(2-diphenylmethylaminocarbonylethyl)naphthalene.
1-tetrazolylmethoxy-5-(2-diphenylmethylaminocarbonylethyl)naphthalene,
1-methoxy-5-[2-[1-phenyl-1-(3-chlorophenyl)methyl]aminocarbonylethyl]-naphthalene,
5-[2-[1-phenyl-1-(3-chlorophenyl)methyl]aminocarbonylethyl]naphth-1-ol or
1-cyanomethoxy-5-[2-[1-phenyl-1-(3-chlorophenyl)methyl]aminocarbonylethyl]-naphthalene.

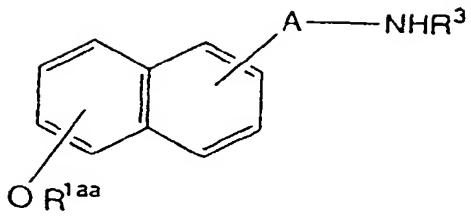
9. A process for the preparation of a naphthyloxyacetic acid derivative of formula (I) as defined in claim 1 or a non-toxic salt, non-toxic acid addition salt or hydrate thereof which comprises:

(a) when the compound of formula (I) conforms to the formula (Ia)



(Ia)

wherein R^{1a} is C1-4 alkyl or (C1-4 alkylene)-$COOR^{10}$ in which R^{10} is as defined in claim 1 and the other symbols are as defined in claim 1,
reacting a compound of the formula (II)



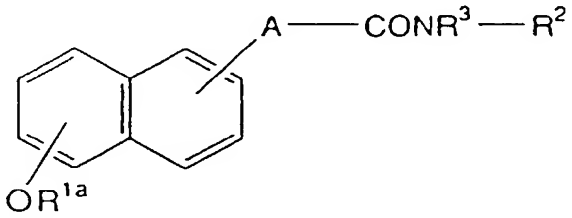
(II)

wherein R^{1aa} is C1-4 alkyl or (C1-4 alkylene)-$COOR^{10a}$ in which R^{10a} is C1-4 alkyl, and the other symbols are as hereinbefore defined with a compound of the formula (III)

$$HOOC\text{-}R^2 \qquad \text{(III)}$$

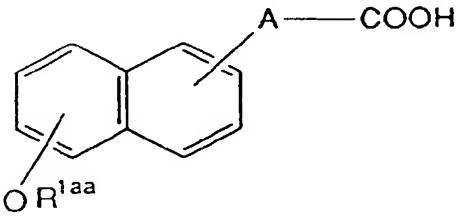
wherein R^2 is as hereinbefore defined to form an amide-bond, optionally followed by hydrolysis under alkaline conditions;

(b) when the compound of formula (I) conforms to the formula (Ib)



(Ib)

wherein all symbols are as hereinbefore defined, reacting a compound of the formula (IV)



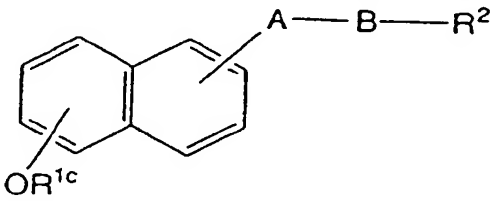
(IV)

wherein all symbols are as hereinbefore defined with a compound of the formula (V)

$$R^3HN\text{-}R^2 \qquad \text{(V)}$$

wherein all symbols are as hereinbefore defined to form an amide-bond, optionally followed by hydrolysis under alkaline conditions;

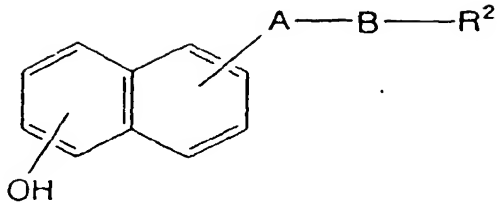
(c) when the compound of formula (I) conforms to the formula (Ic)



(Ic)

wherein, R^{1c} is (C1-4 alkylene)-$COOR^{10}$, (C1-4 alkylene)-OH, (C1-4 alkylene) -$CONR^4R^5$, (C1-4 alkylene) -$CONR^6$- (C1-4 alkylene)-OH, (C1-4 alkylene) -NR^4R^5, (C1-4 alkylene)-cyano or (C1-4 alkylene)-tetrazolyl as defined in claim 1, and the other symbols are as defined in claim 1,

reacting a compound of the formula (Id)



(Id)

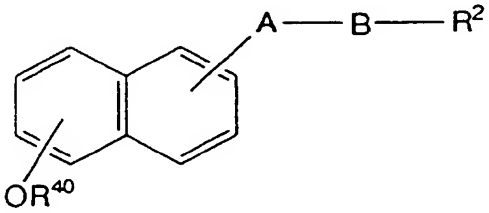
wherein all symbols are as hereinbefore defined with a compound of the formula

$$X^3\text{-}R^{1ca}$$

wherein X^3 is halogen and R^{1ca} is

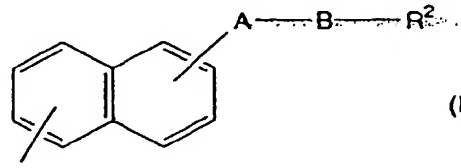
(C1-4 alkylene)-$COOR^{10a}$,
(C1-4 alkylene)-OR^{30a},
(C1-4 alkylene)-$CONR^4R^{5a}$,
(C1-4 alkylene)-$CONR^6$-(C1-4 alkylene)-OR^{30a},
(C1-4 alkylene)-NR^4R^{5a},
(C1-4 alkylene)-cyano or
(C1-4 alkylene)-tetrazolyl-R^{30a}

in which, R^{5a} is C1-4 alkyl, benzyloxycarbonyl or t-butoxycarbonyl, R^{30a} is tetrahydropyranyl, benzyloxycarbonyl or t-butoxycarbonyl, and the other symbols are as hereinbefore defined, optionally followed by hydrolysis under alkaline conditions or by removal of the protecting group;
(d) when the compound of formula (I) conforms to the formula (Ic) wherein R^{1c} is (C1-4 alkylene)-tetrazolyl and the other symbols are as defined in claim 1, reacting a compound of formula (Ic) wherein R^{1c} is (C1-4 alkylene)-cyano and the other symbols are as hereinbefore defined, with sodium azide;
(e) when the compound of formula (I) conforms to the formula (Id) wherein all symbols are as defined in claim 1, reducing or removing alkyl from a compoound of the formula (XIII)



(XIII)

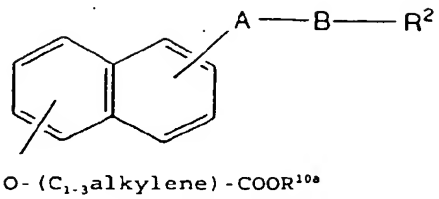
wherein R^{40} is C1-4 alkyl or benzyl and the other symbols are as hereinbefore defined;
(f) when the compound of formula (I) conforms to the formula (Ie)



(Ie)

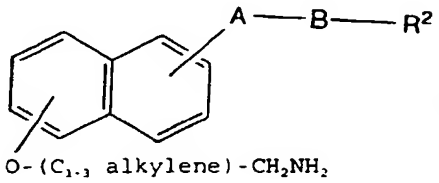
O-(C_{1-3}alkylene)-CH_2OH

wherein all symbols are as defined in claim 1, reacting a compound of the formula (XVIa)



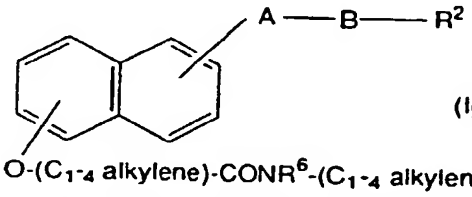
(XVIa)

wherein all symbols are as hereinbefore defined with $NaBH_4$ or $LiBH_4$;
(g) when the compound of formula (I) conforms to the formula (If)



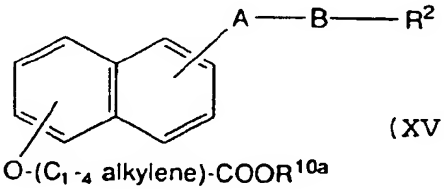
(If)

wherein all symbols are as defined in claim 1, reacting a compound of the formula (Ie) wherein all symbols are as hereinbefore defined with NaN_3 followed by reduction;
(h) when the compound of formula (I) conforms to the formula (Ig)



(Ig)

wherein all symbols are as defined in claim 1, reacting a compound of the formula (XVIb)

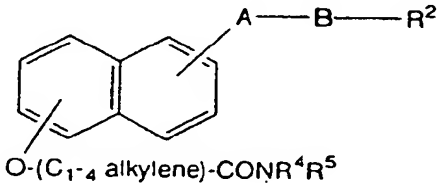


(XVIb)

wherein all symbols are as hereinbefore defined with a compound of the formula

$$HR^6N\text{-(C1-4 alkylene)-OH}$$

wherein all symbols are as hereinbefore defined under alkaline conditions; or
(i) when the compound of formula (I) conforms to the formula (Ih)



(Ih)

wherein all symbols are as defined in claim 1, reacting a compound of the formula (XVIb) wherein all symbols are as hereinbefore defined with a compound of the formula

$$HNR^4R^5$$

wherein all symbols are as hereinbefore defined under alkaline conditions; and
(j) optionally converting a compound of formula (I) thus obtained into a non-toxic salt, non-toxic acid addition

salt or hydrate thereof.

10. A pharmaceutical composition which comprises a naphthyloxyacetic acid derivative of formula (I) as defined in claim 1, or a non-toxic salt, non-toxic acid addition salt or hydrate thereof, in association with a pharmaceutically acceptable carrier or coating.

11. Use of a naphthyloxyacetic acid derivative of formula (I) as defined in claim 1, or a non-toxic salt, non-toxic acid addition salt or hydrate thereof, in the manufacture of a medicament for the treatment and/or prevention of abortion, pain, diarrhea, catharsis, ulcers, gastritis, hypertension or thrombosis, or in the manufacture of a medicament for the induction of abortion or sleep.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 95 30 9493

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 603 953 (EASTMAN KODAK CO) 29 June 1994 * preparation C, D; page 9, line 32, 36, 38, 52; page 10, line 7 * ---	1,3,4	C07C235/34 C07C243/22 C07C235/66 C07D213/40 C07C255/12
X	CHEMICAL ABSTRACTS, vol. 107, no. 23, 7 December 1987 Columbus, Ohio, US; abstract no. 217466, V. V. MEZHERITSKII ET AL. page 574; * abstract * & ZH. ORG. KHIM., vol. 22, no. 11, 1986 pages 2394-2398, ---	1,3,4	C07D257/04 A61K31/21 A61K31/165 A61K31/19 A61K31/44 A61K31/275 A61K31/41
X	WO-A-84 04245 (RORER INT OVERSEAS) 8 November 1984 * page 40, line 1 - line 9 * ---	1,3,4	
	-/--		TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07C C07D

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	12 April 1996	Seufert, G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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EPO FORM 1503 03.82 (P04C07)

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Application Number EP 95 30 9493

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	SYNTHESIS, no. 5, 1983 STUTTGART DE, pages 385-6, L- A. CATE 'An efficient carboxylation of 1-naphthols using magnesium methyl carbonate' * page 385, compound 2f, 2g * ---	1,3,4	
X	CHEMICAL ABSTRACTS, vol. 94, no. 15, 13 April 1981 Columbus, Ohio, US; abstract no. 121225, V. V. MEZHERITSKII ET AL. page 669; * abstract * & ZH. ORG. KHIM., vol. 16, no. 9, 1980 pages 1958-64, ---	1,3,4	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	FR-A-2 059 962 (IMPERIAL CHEMICAL INDUSTRIES) 11 June 1971 * page 7, line 15 * * page 8, line 3 - line 4 * ---	1,3,4	
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 20, 1994 WASHINGTON US, pages 3231-39, P. DEPREUX ET AL. 'Synthesis and structure-activity relationships of novel naphthalenic and bioisosteric related amidic derivatives as melatonin receptor ligands' * page 3234, table 1, example 36 ---	1,3,4	
	-/--		

EPO FORM 1503 03.82 (P04C10)

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PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 95 30 9493

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, no. 8, 1991 WASHINGTON US, pages 2504-20, J. WROBEL ET AL. 'Synthesis of tolrestat analogues containing additional substituents in the ring and their evaluation as aldose reductase inhibitors.' * page 2507, compound 33 * ---	1,3,4	
X	JOURNAL OF ORGANIC CHEMISTRY, vol. 52, no. 15, 1987 EASTON US, pages 3181-5, R. D. BINDAL ET AL. 'Steric factors in amide-directed metalations of N,N-Dialkyl-6-methoxynaphthalene-2-carboxamides: synthesis of a sterically perturbed acylnaphthol' * page 3182, compounds 7, 8, 9 * ---	1,3,4	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	CHEMICAL ABSTRACTS, vol. 99, no. 13, 26 September 1983 Columbus, Ohio, US; abstract no. 104938, S. A. JACOBS ET AL. page 558; * RN 86896-03-9, 1-Naphthalenecarboxamide, 6-methoxy -N,N-dimethyl * & CARCINOGENESIS, vol. 4, no. 5, 1983 pages 519-22, ---	1,3,4	
X	US-A-4 327 022 (BAILEY DENIS M) 27 April 1982 * column 54, line 66 - line 67 * --- -/--	1,3,4	

EPO FORM 1503 03.82 (P04C10)

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PARTIAL EUROPEAN SEARCH REPORT

Application Number EP 95 30 9493

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	CHEMICAL ABSTRACTS, vol. 91, no. 14, 1 October 1979 Columbus, Ohio, US; abstract no. 115338, TAMURA, HIROSHI ET AL. page 513; * RN 70938-68-0, 1-Naphthalenecarboxamide, N-hexyl-6- hydroxy- * & JP-A-79 030 023 (RICOH CO.) ---	1,3,4	
X	CHEMICAL ABSTRACTS, vol. 83, no. 25, 22 December 1975 Columbus, Ohio, US; abstract no. 206008, NOGUCHI, SHUNSAKU ET AL. page 369; * RN 57382-60-2, Acetamide, N-[(6-methoxy-1-naphthale nyl)methyl] * * RN 57382-52-2, 1-Naphthalenecarboxamide, 6-methoxy -N-methyl- * & JP-A-75 089 352 (TAKEDA CHEMICAL INDUSTRIES) ---	1,3,4	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	DE-A-24 13 986 (HODOGAYA CHEMICAL CO LTD ;FUJI PHOTO FILM CO LTD (JP)) 28 November 1974 * Table I, compound V, page 16, 33 - 35 * ---	1,3,4	
	-/--		

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Application Number EP 95 30 9493

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	CHEMICAL ABSTRACTS, vol. 82, no. 5, 3 February 1975 Columbus, Ohio, US; abstract no. 27088, G. PAGANI ET AL. page 161; * RN 53803-10-4, 2-Naphthalenecarboxamide, 6-methoxy -N,N-bis(1-methylpropyl)- & FARMACO, ED. SCI., vol. 29, no. 7, 1974 pages 491-506, ---	1,3,4	
X	JOURNAL OF ORGANIC CHEMISTRY, vol. 26, 1961 EASTON US, pages 3086-9, N. A. NELSON ET AL. 'Steroidal hormone analogs. IX. Bisdehydrodoisynolic acid analogs possessing the 1,2,3,4-Tetrahydrobenz[f]isoquinoline nucleus' * page 3087, compound IIa * ---	1,3,4	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	GB-A-899 714 (IMPERIAL CHEMICAL INDUSTRIES) 27 June 1962 * table page 7, coupling compound in ex. 14, 20 * ---	1,3,4	
A,D	EP-A-0 542 203 (ONO PHARMACEUTICAL CO) 19 May 1993 * claims; examples * ---	1-11	
A	EP-A-0 512 399 (SEARLE & CO) 11 November 1992 * page 37, line 47 - page 40, line 44 * -----		

EPO FORM 1503 03.82 (P04C10)

EP 95 30 9493
-C-

Claims searched completely: 6-8

Claims searched incompletely: 1-5,9-11

The variable attachment points of the substituents A-B-R2 and O-R1 in combination with a broad definition of the value of the variables preclude a comprehensive search. For economic reasons the search has been limited. Search and search report can be considered complete for the following case: the substituent A-B-R2 is attached either in position 1 or in position 2 of the naphthyl ring with the oxygen atom of OR1 attached to position 5 or 6.